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OXIDATION OF ALKENES TO ALLYLIC HYDROPEROXIDES

BY

© WAYNE ALLAN SCOTT

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1973

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled, OXIDATION OF ALKENES TO ALLYLIC HYDROPEROXIDES submitted by Wayne Allan Scott, in partial fulfilment of the requirements for the degree of Master of Science.

Karl B. Kopecky
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Dennis N. James

Larry Bowo

Date Fall 1973

TO MY MOTHER AND FATHER

ABSTRACT

The tetrasubstituted olefin, isopropylidenecyclohexane 5 was synthesized and its β-halohydroperoxides, 1-(methyl-1-hydroperoxyethyl)-cyclohexyl bromide 7, iodide 8, and chloride 9 were prepared and treated with base. Two allylic hydroperoxides were obtained, 1-(methylvinyl)-cyclohexyl hydroperoxide 15 and 1-(methyl-1-hydroperoxyethyl)-cyclohexene 16 in a 16/15 ratio of 15.7, 15.7 and 13.3 respectively. These product ratios were independent of halogen atom, solvent polarity, temperature and dilution effects. The hydroperoxy migration was explained in terms of a perepoxide intermediate. A similar migration was observed upon treatment of 1-(methyl-1-bromoethyl)-cyclopentyl hydroperoxide 25.

The 16/15 ratio of allylic hydroperoxides obtained from the dye-sensitized photooxidation of 5 was found to be 0.11. This reaction was observed to be less regiospecific for more reactive olefins. This conclusion was substantiated when the dye-sensitized photooxidation of isopropylidenecyclopentane 23, a more reactive olefin, gave a ratio of allylic hydroperoxides of 0.62.

Only one allylic hydroperoxide, 15, was obtained as the product from the reaction of 5 with triphenyl phosphite ozonide at -78°. This reaction does not proceed via a singlet oxygen mechanism and is a more regioselective reaction than the dye-sensitized photooxidation.

The formation of 16 as the major product from 7 and 15 from the triphenyl phosphite ozonide reaction may lead to a useful sythnetic preparation of either of two possible allylic hydroperoxides from an unsymmetrical alkene.

ACKNOWLEDGEMENTS

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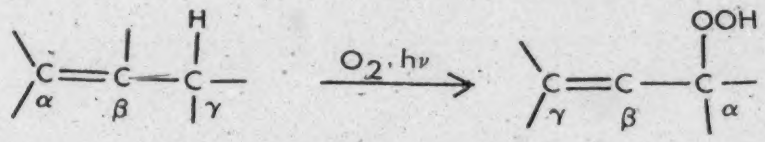
INTRODUCTION

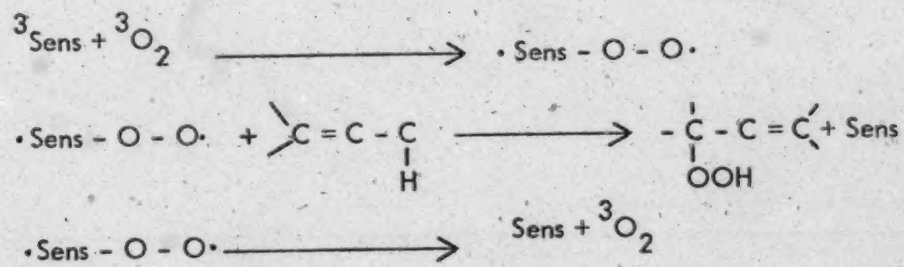
This investigation was undertaken as part of a research program aimed at studying the mechanism of the reactions leading to the formation of allylic hydroperoxides. Much of the previous work pertaining to the dye-sensitized oxidation of olefins has been reviewed by van de Sande (1).

Schenck's group has been instrumental in the development of the process leading to the formation of allylic hydroperoxides from the dye-sensitized reaction of an olefin with oxygen (2). In the photooxygenation of olefins, the oxygen transferred is added to the carbon α of the double bond; the double bond is shifted into the allyl position to form a double bond between carbon β and γ and the allylic hydrogen at carbon γ is moved to the free oxygen atom (2).

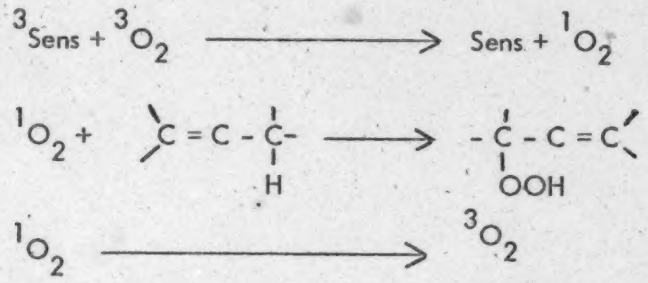


Tetramethylethylene reacts under the conditions of the dye-sensitized photooxygenation to give 3-hydroperoxy-2,3-dimethyl-1-butene (2).

Schenck's original work gave rise to two mechanisms of the reaction of oxygen with sensitizer. The first involves the formation of an oxygen sensitizer complex.



The other mechanism involves the formation of singlet oxygen ($^1O_2$) from the sensitizer in the triplet state and oxygen (3).



The bulk of the evidence now points to singlet oxygen, not the oxygen sensitizer complex as the reactive intermediate.

Sharp (4) and Kopecky (5) found that increasing substitution of the double bond greatly increased the reactivity towards oxidation. A sensitizer complex cannot account for this. Kopecky (5) found that varying the sensitizer did not affect the relative rates of photooxidation of 1-methylcyclopentene and 1-methylcyclohexene. This independence of sensitizer and the relative rates of photooxidation of olefins was also found by Schenck and Koch (6) in the dye-sensitized oxidation of α-terpinene.

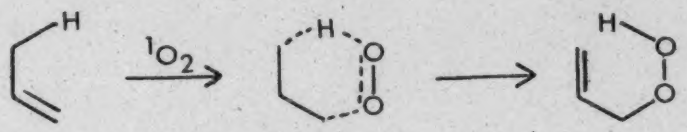
Support for singlet oxygen as the reactive intermediate was given by Foote (7, 8). Identical products to those formed in the dye-sensitized photooxidation are produced when olefins are treated with sodium hypochlorite and hydrogen peroxide, a chemical source of singlet oxygen. Autoxidation in these singlet oxygen reactions could be suppressed by the presence of a free radical inhibitor, 2,6-di-t-butylphenol (9).

Spectroscopic studies have detected the formation of singlet oxygen in the photosensitized oxidation of naphthalene (10,11).

The mechanism of the approach of singlet oxygen to the double bond has been studied quite extensively by Nickon and his group (12, 13, 14, 15, 16). Nickon concluded that the reaction was very stereospecific, showed no solvent dependence and required an axial hydrogen on the same side as where the oxygen came in. In other words, the singlet oxygen must necessarily

attack the π-orbital from a direction perpendicular to the olefinic plane and the allylic hydrogen must be suitably orientated to allow transfer to oxygen.

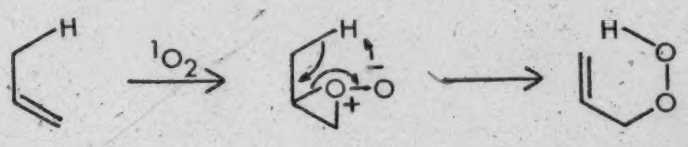
A concerted mechanism was proposed by Nickon.



Foote (17, 18, 19, 20, 21) finds support for this mechanism by the smooth shift of the double bond, cis relationship of the allylic hydrogen, lack of substituent or Markovnikov effects on the product distribution, and the lack of solvent effects on the rate.

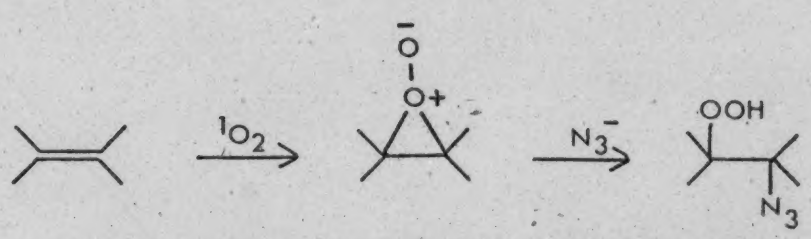
Klein and Rojahn (22) showed the dye-sensitized photooxygenation of exocyclic double bonds was highly sterically controlled. Methylenecyclohexane and methylenecyclopentane could not be oxygenated while methylenecycloheptane and β-pinene produced the expected allylic hydroperoxides. They suggested that the distance between the vinyl carbon and the axial or quasi-axial allylic hydrogen is too large to form a cyclic transition state in the case of methylenecyclopentane and methylenecyclohexane.

Sharp (4) and Kopecky (5) explained the different reactivities of a series of alkenes by the formation of an intermediate perepoxide which rearranges with a concurrent proton shift to yield allylic hydroperoxides.



The perepoxide mechanism was given support by the observation that added sodium azide diverts most of the products of photooxygenation of several olefins to azidohydroperoxides (23). Kearns (24) interpreted these new products as being formed from the perepoxide by nucleophilic reaction with azide ion, equation [1]

[1]

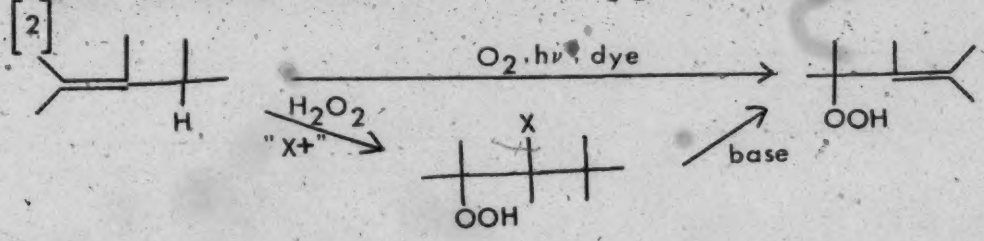


Both Foote (25) and Gollnick (26) have presented evidence that azidohydroperoxides are formed in a reaction which competes with, but is distinct from the normal oxygenation and that no intermediate formed from singlet oxygen with the olefin is common to both reactions.

Photooxygenation of olefins for which the six-membered cyclic mechanism is not applicable on steric grounds have been shown to give a stable, isolable 1,2-dioxetane (27). The original suggestion (28) that a 1,2-dioxetane was the intermediate leading to allylic hydroperoxides has been ruled out by the results of Kopecky and Mumford (29, 30), that isolated dioxetanes do not decompose to allylic hydroperoxides.

The work of van de Sande (1) was instrumental in using the reaction between base and 2-halohydroperoxides as an alternate method to the sensitized photooxidation route of preparing allylic hydroperoxides. Methods for preparing 2-halohydroperoxides had been known (31, 32, 33). Kopecky and co-workers (34) introduced a method for preparing 2-halohydroperoxides in clean, high-yield reactions by treating olefins with N-haloacetamides and hydrogen peroxide. Treatment of a tetrasubstituted olefin in this fashion and reaction of the product with base introduces the hydroperoxy group and shifts the double bond of an olefin into the same position as observed in the photosensitized reaction (1, 30, 34), equation [2].

[2]

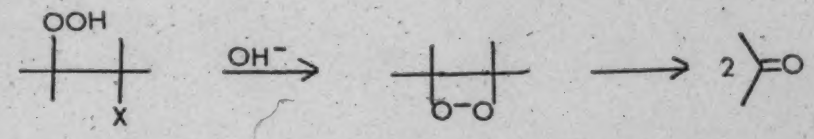


Essentially the same distribution of products is formed from the halohydroperoxides of 1,2-dimethylcyclohexene (34) and 2-methyl-3-(4-methoxyphenyl)-2-butene (3) as formed by the oxidation of these alkenes by singlet oxygen.

The formation of allylic hydroperoxides from halohydroperoxides is not a general reaction. No trace of allylic hydroperoxides is found in the reaction between base and less substituted 2-halohydroperoxides (1, 30, 34). A variety of products is observed.

The formation of cleavage products (30, 34, 35) indicated that a cyclic peroxide may be formed as an intermediate, equation [3].

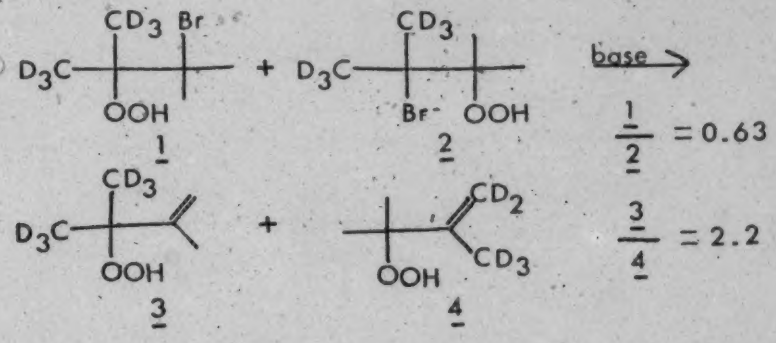
[3]



The reaction of trimethyl-1,2-dioxetane with base shows no allylic hydroperoxides as products (30, 36). Cleavage products have not been observed in the reaction between the β-halohydroperoxides of tetrasubstituted olefins and base (30, 34). These two results tend to eliminate a 1,2-dioxetane intermediate in the formation of allylic hydroperoxides.

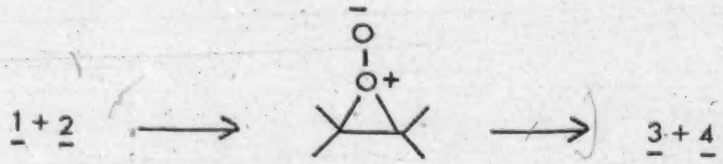
The observation of van de Sande (1), that the hydroperoxy group of β-bromohydroperoxides migrates in the presence of base, equation [4] led to the postulation of non-direct elimination mechanisms leading to the formation of allylic hydroperoxides.

[4]



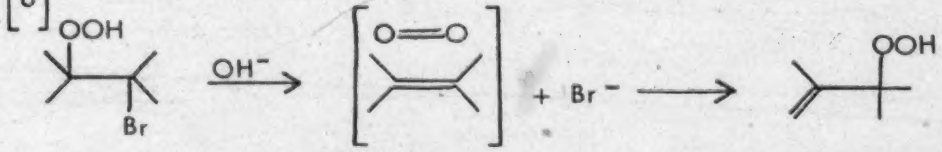
The first mechanism proposed was the formation and subsequent reorganization of a perepoxide leading to a possible migration of the hydroperoxy group, equation [5]

[5]

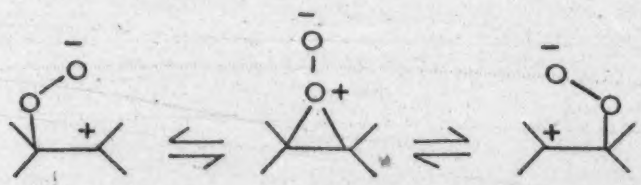


Van de Sande (1) failed to trap this perepoxide with azide ion and failed to observe this intermediate spectroscopically . The second possible mechanism involved a fragmentation and eventual reaction of the olefin with singlet oxygen, equation [6] .

[6]



Van de Sande provided strong evidence against this mechanism. Finally, a possible mechanism was proposed (1) wherein an open chain zwitterion plays a role in the conversion of 2-bromohydroperoxides to allylic hydroperoxides.



They would interconvert via the perepoxide. However, evidence against this mechanism has also been presented by van de Sande (1). He did not observe any substituent effects that should affect product distribution via these intermediate zwitterions.

Triphenyl phosphite ozonide (37) has been shown to oxidize tetramethylethylene to the corresponding allylic hydroperoxide at -30° and to decompose to triphenyl phosphate and singlet oxygen at -15° (38, 39). It was suggested that tetramethylethylene was oxidized by the singlet oxygen

released. It has been shown that singlet oxygen does not intervene in the triphenyl phosphite ozonide oxygenation at low temperatures (40) so that still another mechanism is required for oxygenation by this reagent. Van de Sande (1) observed that the product distribution in the oxidation of a deuterated olefin by triphenyl phosphite ozonide at -70° in methylene chloride was quite similar to those observed in singlet oxygen oxidation at -52° in methanol. This indicated that a perepoxide intermediate could not be involved.

The present study was made in an attempt to distinguish several possibilities for the mechanism that could be envisaged for the transformation of β-halohydroperoxides to allylic hydroperoxides. In addition, it was of interest to determine whether this reaction and the reaction between singlet oxygen and a tetrasubstituted olefin have common intermediates as well as products. The product distributions were determined for the conversion of isopropylidenecyclohexane 5 to the corresponding allylic hydroperoxides by the routes: 1) reaction between its β-halohydroperoxides and base; 2) by oxidation with singlet oxygen generated by methylene blue-sensitization and 3) by oxidation with triphenyl phosphite ozonide.

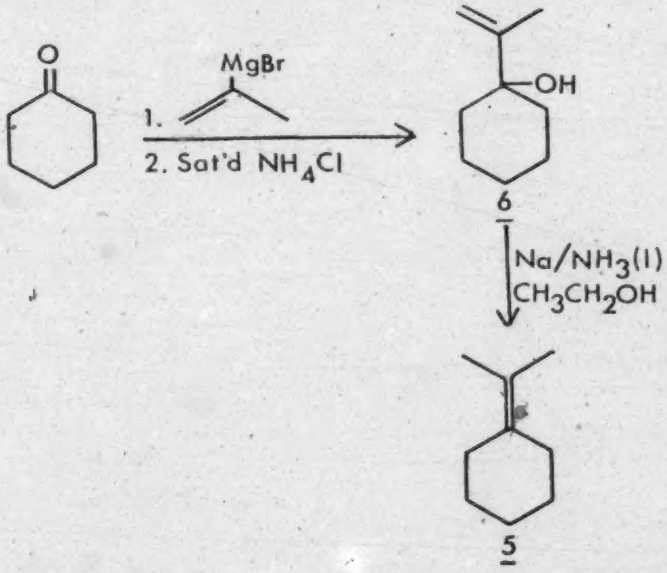
Isopropylidenecyclohexane 5 was chosen as a model compound for these reactions for several reasons. First, it is a tetrasubstituted olefin and thus it should be reactive towards attack by singlet oxygen (5). Second, with this olefin, the geometric requirements of a cyclic transition state can be tested by observing the products obtained from the dye-sensitized oxygenation. Third, more information concerning the mechanism involved in the oxidation of olefins with triphenyl phosphite ozonide may be obtained by observing the stereochemistry of the products obtained in this reaction. Finally, this unsymmetrical olefin can be useful in determining the extent of hydroperoxy migration when its corresponding β-halohydroperoxides are treated with base.

RESULTS

Preparation of isopropylidenecyclohexane, 5:

A method for the preparation of 5 in large quantities was developed. Attempts to synthesize this olefin from vicinal dihalo (41), dinitro (42) and dihydroxy (43) derivatives proved unsuccessful in producing useful quantities. The sequence of reactions employed for the preparation of 5 is outlined in Scheme I.

SCHEME I



This method resembles the synthesis of ethylidenecyclohexane by Birch (44). The route used incorporated the Grignard reagent prepared from 2-bromopropene (45).

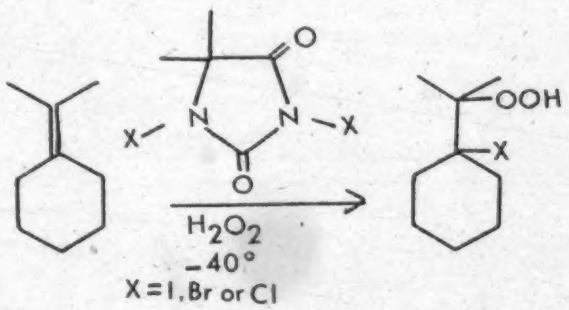
Due to the sensitivity of the intermediate, 1-(methylvinyl)-cyclohexanol 6, the reaction mixture was worked up with saturated ammonium chloride and 6 was purified by distillation from neutralized glassware. The structure of 6 obtained in a 66% yield, was carefully confirmed by its n.m.r. spectrum, i.r. spectrum, microanalysis and mass spectrum.

Reduction of 6 was carried out in the presence of two equivalents of sodium and ethanol in liquid ammonia. Maximum yield from the reduction was 72% and was less if 6 was not previously distilled. The structure of the olefin 5 was confirmed by comparison of its boiling point, refractive index and i.r. spectrum with reported data (41), and by its n.m.r. spectrum. The olefin could be stored under nitrogen for indefinite periods with no visible change as detected by n.m.r. spectroscopy.

Preparation of the β-halohydroperoxides of isopropylidenecyclohexane:

The reaction between 5, one equivalent of 1,3-dihalo-5,5-dimethylhydantoin and a four fold excess of hydrogen peroxide in ether at -40° proceeded readily, using an adaptation of the procedure of Mumford (30), equation [7]

[7]



The β-bromo compound, 1-(methyl-1-hydroperoxyethyl)-cyclohexyl bromide 7, contained 76% of theoretical peroxide after solvent removal and this was increased to 99.7% by recrystallization from Skelly B.

The corresponding iodohydroperoxide, 1-(methyl-1-hydroperoxyethyl)-cyclohexyl iodide 8, contained 67% peroxide content after solvent removal and this could be improved to 98% by recrystallization from Skelly B.

For the preparation of 1-(methyl-1-hydroperoxyethyl)-cyclohexyl chloride 9, a slight modification of this procedure was used. The iodo- and bromohydroperoxides could be prepared by using a four fold excess

of hydrogen peroxide in varying amounts of solvent. Although at least a four fold excess of hydrogen peroxide was needed for the preparation of 9, a more polar solvent system had to be used. This was accomplished by using a solution composed of 25% hydrogen peroxide in ether. Repeated low temperature recrystallizations produced a sample of 9 containing 100% theoretical peroxide content.

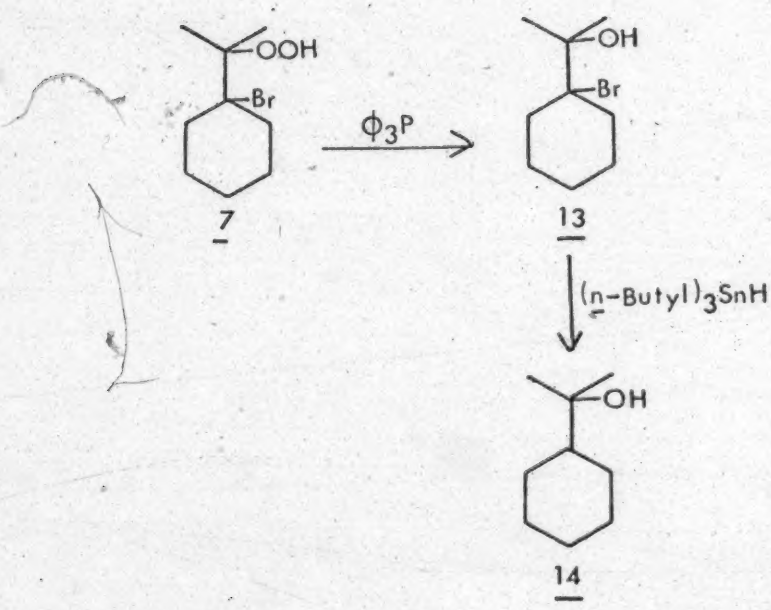
Preliminary structural assignments of these β-halohydroperoxides were made by n.m.r. spectroscopy. The signal for the gem-dimethyl protons of these compounds, 7, 8 and 9, α to a hydroperoxy and β to a halogen atom was compared to the signals of similar protons in known compounds. The gem-dimethyl groups of 7, 8, and 9 appeared at τ 8.5, τ 8.6 and τ 8.4, respectively.

The corresponding signals for 2-chloro-2,3-dimethyl-3-butyl hydroperoxide 10 appeared at τ 8.60; the other gem-dimethyl group appeared as a singlet τ 8.38 (1). The corresponding gem-dimethyl singlet for 2-bromo-2,3-dimethyl-3-butyl hydroperoxide 11 appeared at τ 8.55; the other singlet for the gem-dimethyl group α to a bromine and β to a hydroperoxy group appeared at τ 8.19 (1).

The corresponding singlet for 2-iodo-2,3-dimethyl-3-butyl hydroperoxide 12 appeared at τ 8.55; the signal for the other gem-dimethyl group appeared at τ 8.0 (46). There was no evidence in the n.m.r. spectrum of crude 7 for the gem-dimethyl group of the corresponding dibromide (41). Chemical determination of the structure of 7, i.e. the position of the bromine, was carried out because products obtained from this compound and the analogous iodo- and chlorohydroperoxides had to be interpreted in terms of the exact position of the halogen atom. This was carried out by the sequence of reactions outlined in Scheme II.

The reduction of hydroperoxides by triphenylphosphine is known to proceed with no structural rearrangement (47). Bromohydroperoxides have been reduced virtually quantitatively by this method to yield bromohydrins (46).

SCHEME II

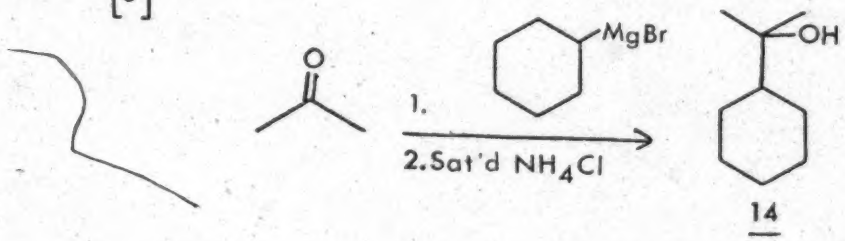


7 → 13 → 14

The reduction of 7 to the corresponding bromohydrin 13 was carried out in Skelly B by this method. Purification of the product could be carried out readily by chromotography on silica gel. The yield of bromohydrin produced in this way was 90%, and the structural assignment was based on the n.m.r. spectrum.

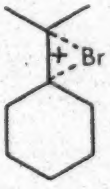
Non-distilled tri-n-butyltin hydride, prepared according to the procedure of Kuivila (48), was used for the debromination of 13. This reagent was expected to carry out dehalogenation without migration of the hydroxy group (49). Preliminary experiments carried out at room temperature showed debromination of 13 to be incomplete. Using refluxing benzene, the crude yield of dimethylcyclohexylcarbinol 14 was 87%. Chromatography on silica gel was used to eliminate tin containing impurities. The infrared and n.m.r. spectra were identical to those of 14 prepared independently, equation [8].

[8]



14

1,3-Dibromo-5,5-dimethylhydantoin is known to be a positive halogen donor (50). The formation of 7 from isopropylidenecyclohexane could be expressed as a two step process: the electrophilic addition of a "Br^+" to the double bond to give an unsymmetrical bromonium ion (51), shown below, followed by attack by the nucleophilic hydrogen peroxide to give 7.



The formation of the β-bromohydroperoxide 7 by this method is consistent with the results obtained by Sisti (51). He found that treatment of 5 with N-bromosuccinimide and water resulted in the formation of 13. Our structure proof for the relative positions of the bromine and hydroperoxy group confirms the positions of the bromine and hydroxy groups of 13 assigned by Sisti (51).

Preparation of 1-(methylvinyl)-cyclohexyl hydroperoxide, 15, and 1-(methyl-1-hydroperoxyethyl)-cyclohexene, 16:

The products from the reaction of the β-halohydroperoxides of 5 with base were expected to be 15 and 16. For the analysis of product mixtures containing these compounds, it was necessary to prepare and isolate authentic samples of 15 and 16. Preliminary experiments showed that treatment of 5 with triphenyl phosphite ozonide in methylene chloride at -78° produced 15 virtually quantitatively. This method was then employed as a direct route to the preparation and ultimate isolation of authentic samples of 15.

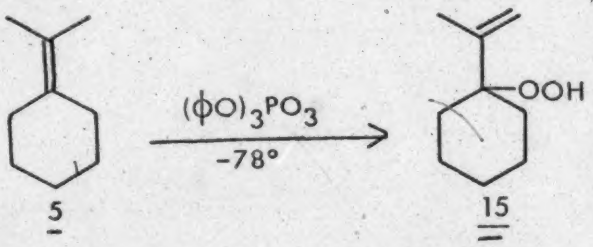
The reaction was carried out using the conditions adapted from the procedure of Bartlett and Mendenhall (40). Addition of triphenyl phosphite to ozone in methylene chloride at -78° had to be sufficiently slow to avoid decomposition of the ozonide to triphenyl phosphate, equation [9].

[9] $$(\phi O)_3PO_3 \xrightarrow{(\phi O)_3P} (\phi O)_3PO$$

The yield of 15, virtually quantitative, was determined in a control run by n.m.r. spectroscopy using p-dimethoxybenzene as an internal standard. The area of the vinylic protons was compared to the area of the signals obtained from the internal standard. Purification of the product was accomplished by chromatography on silica gel, followed by repeated recrystallization from isopentane at -78°. The white solid obtained, contained

99.5% of the theoretical peroxide content. The formation of 15 is shown in equation [10].

[10]



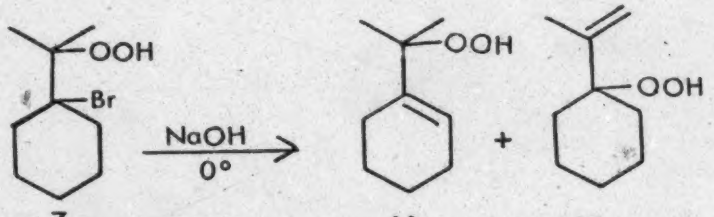
5 15

Final structural assignment was carried out by reduction of 15 with $LiAlH_4$ to the corresponding allylic alcohol 6 in a 94% yield. The n.m.r. spectrum of the reduction product was identical to the spectrum of 6 prepared via the Grignard reagent.

The n.m.r. spectra of the allylic hydroperoxide 15 and the allylic alcohol 6 are given in the experimental section. It should be noted that the vinylic protons of the hydroperoxide 15 appear as a singlet at τ 5.05 while the vinylic protons of the corresponding alcohol appear as two singlets centred at τ 5.15, separated by 13 cps.

Preliminary reaction of 7 with base showed the presence of 16 in substantial yields along with varying small amounts of 15. Because of this result, this reaction, shown in equation [11], was used to synthesize 16.

[11]



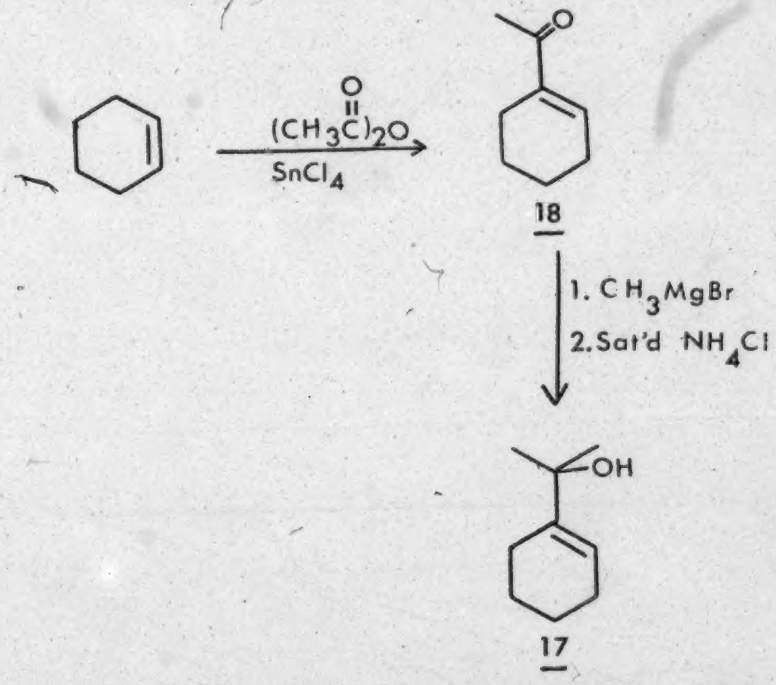
7 16 15

Elimination of HBr from 7 by treatment with base was carried out smoothly at 0° by the method outlined by Mumford (31). Again addition of an internal standard, p-dimethoxybenzene, was used to determine the yield

of 16 by comparison of the area of the singlet at τ 8.75 for the gem - dimethyl group of 16 to the area of the internal standard peaks. The yield of 16 calculated in this way was 92%. Repeated recrystallization at -78° gave a sample of 16 containing 99.7% of the theoretical active oxygen content. By inspection of the vinylic region of the n.m.r. spectrum, this sample of 16 was free of any 15 produced in this reaction.

The final structural assignment was made by comparing the $LiAlH_4$ reduction product of 16 with 1-(methyl-1-hydroxyethyl)-cyclohexene 17 prepared via an independent synthesis outlined in Scheme III.

SCHEME III



The n.m.r. spectrum of the allylic alcohol 17, prepared from the reduction of the allylic hydroperoxide, was identical to that of the allylic alcohol prepared independently.

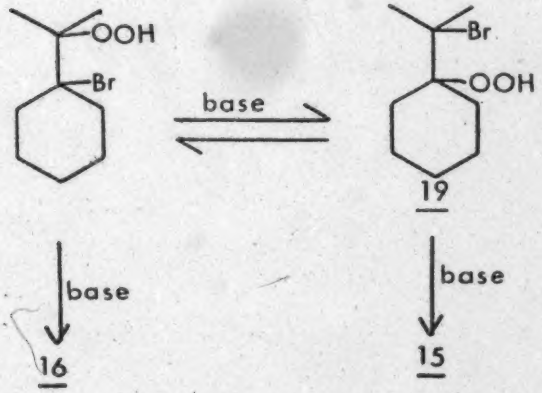
Reaction of β -halohydroperoxides with base:

When it was first observed that 15 was formed from the reaction of

7 with base, further investigation of this reaction was carried out to obtain information regarding the possible mechanisms for migration of the hydroperoxy group. The reactions of 8 and 9 with base were carried out to observe what the effect of changing the halogen atom had on the product distribution. This was done when it was observed that the 16/15 ratio, obtained from the reaction of crude 7 with base, was significantly different from that obtained from the reaction of 8 with base. In addition to changing the halogen atom, the effect on the 16/15 ratio by varying temperature, concentrations, solvent polarity and base were determined in the hope that these experiments would furnish additional information about the possible reaction mechanism involved.

The presence of 15 in the product mixture could possibly arise from the isomerization of 7 during the course of the reaction. The isomerization product, structure 19 in Scheme IV, could yield 15 upon direct elimination of HBr.

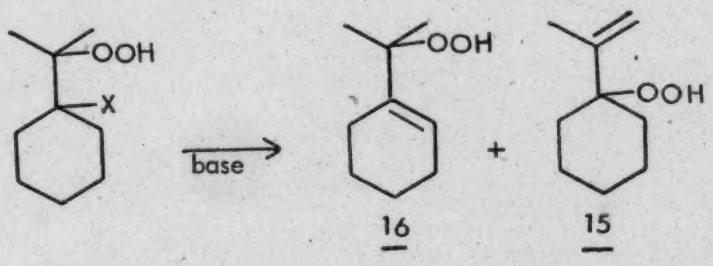
SCHEME IV



This was a possible mechanism that could explain the presence of 15 in the product mixture without migration of the hydroperoxy group. This pathway to the formation of 15 was ruled out when it was observed that the n.m.r. spectrum of the product mixture obtained from the treatment of 7, with 0.5 equivalent of base, run 9, Table I, showed no expected singlet for the gem-dimethyl group of 19. In fact, the n.m.r. spectrum of the product mixture was identical to a mixture of 15 and 16 along with peaks equivalent to unreacted 7.

The general method used to carry out these reactions of β-halo-hydroperoxides with base was adapted from Mumford (30). The formation of allylic hydroperoxides is shown in equation [12].

[12]



16 15

In experiments where at least one equivalent of base was used to react with one equivalent of β-halohydroperoxide, no starting material could be detected in the n.m.r. spectrum of the final product. The yields of allylic hydroperoxides were based on halohydroperoxides and were calculated in the following manner, using the n.m.r. spectra of the product mixtures. An internal standard, p-dimethoxybenzene, was initially added to each reaction mixture. The area of the singlet at τ 8.75, attributed to the gem-dimethyl group of 16 was used to calculate the percentage yield of 16. To this value was added the yield of 15 calculated from the ratio of its vinylic protons peak in the n.m.r. spectrum at τ 5.05 to the vinylic peak of 16 at τ 4.35. The ratios of the areas of these peaks were determined by ampli-

fication of these peaks, followed by three integrations and overaging the integrations obtained. Reproducibility of reactions carried out under identical conditions was ± 0.5%. The 16/15 ratio was also calculated from the average of these three integrations. It should be noted that the vinylic peak for 15 is due to two protons while that for 16 is due to only one proton and consideration of this was taken for the yield and 16/15 ratio calculations.

The reaction of the bromohydroperoxide 7 with base was carried out using the conditions shown in Table I. Runs 1 - 5 were carried out using crude samples of 7. The 16/15 ratio did not vary significantly with solvent polarity or with change of base. The vinylic protons peak attributed to 15 in the n.m.r. spectra, obtained from these first five runs, did not appear as sharp as those obtained from the n.m.r. spectra of pure samples of 15. The yield of allylic hydroperoxides for run 2 (64%) did not account for all the starting material. The high values of 15 were attributed to impurities in the starting material and this accounted for the low 16/15 ratio obtained for runs using crude samples of 7, compared to the 16/15 ratio of 15.7 obtained from the remaining runs using pure samples of 7. For this reason, the overall significance of the results of runs 1 - 5 is questionable and thus runs 2 and 3 were repeated using pure samples of 7. The results are given in runs 6 and 7 and both show a 16/15 ratio of 15.7. Material balance was virtually quantitative and the n.m.r. spectra of these product mixtures showed peaks corresponding to only 16 and 15.

To determine the effect of diluting the reaction, run 7 was carried out using a tenth the concentration of base and 7. Again a 16/15 ratio of 15.7 was obtained from a virtually quantitative reaction and it was concluded that these changes were insignificant.

The effect on the product distribution of changing the halogen atom to iodine was investigated by treating 8 with base under the conditions shown in Table II. Again the n.m.r. spectra of the product mixtures showed

TABLE I

Product Distribution from the Reaction of 1-(Methyl-1-hydroperoxyethyl)-cyclohexyl Bromide, 7 with Base Under Varying Concentrations and Solvents at 0°

Run	Base	Base Conc. [M]	7 [M]	Solvent Composition (%) water	methanol	benzene	ether	yield (%) 16 + 15	16/15
1.	$NaOCH_3$	1.1	1.0	-	100	-	-	-	8.1
2.	NaOH	1.1	1.0	10	90	-	-	64	3.8
3.	NaOH	1.1	1.0	50	50	-	-	-	4.6
4.	NaOH	1.1	1.0	90	-	-	10	-	3.5
5.	*BTMAH	1.1	1.0	-	50	50	-	-	5.7
6.	NaOH	1.1	1.0	10	90	-	-	98	15.7
7.	NaOH	1.1	1.0	50	50	-	-	98	15.7
8.	NaOH	1.1×10^{-1}	1.0×10^{-1}	10	90	-	-	99	15.7
9.	NaOH	5.0×10^{-1}	1.0	10	90	-	-	49	15.7

*BTMAH = Benzyltrimethylammonium hydroxide

Runs 1-5 were carried out using crude samples of 7.

TABLE II

Product Distribution from the Reaction of 1-(Methyl-1-hydroperoxy-ethyl)-cyclohexyl Iodide, 8 with Sodium Hydroxide in 10% Water - 90% Methanol Solutions

Run	NaOH conc [M]	8 [M]	Temp. (°C)	Yield (%) 16 + 15	16/15
1.	1.1	1.0	0	98	15.7
2.	1.1×10^{-1}	1.0×10^{-1}	0	100	15.7
3.	3.75×10^{-3}	1.25×10^{-3}	0	98	15.7
4.	3.75×10^{-3}	1.25×10^{-3}	-40	-	15.7

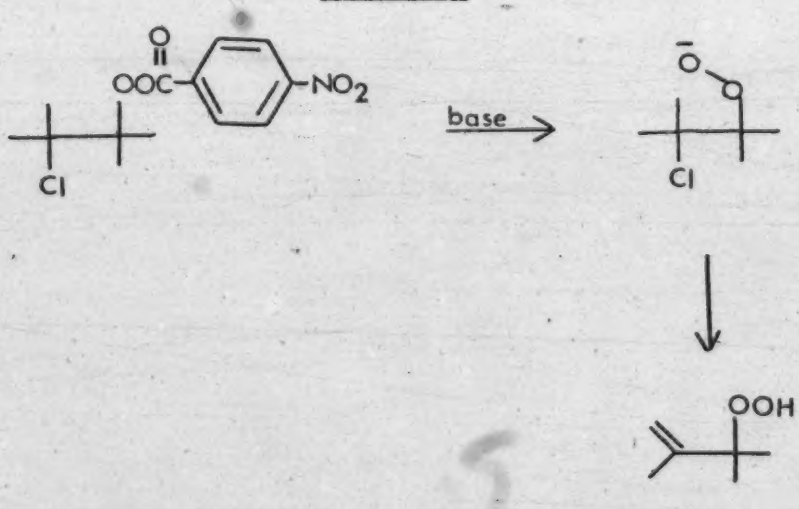
quantitative yields for 16 and 15 and in all runs a 16/15 ratio of 15.7 was obtained. No effect on the 16/15 ratio was observed by dilution of the reaction mixture, increasing the equivalents of base or by decreasing the reaction temperature.

The reaction of 9 with base proceeded virtually quantitatively to the allylic hydroperoxides with a 16/15 ratio of 13.3. The n.m.r. spectrum of the product mixture showed absorptions characteristic of only allylic hydroperoxides 15 and 16. This ratio of 13.3 was not significantly different than the 16/15 ratio of 15.7 obtained from the product mixtures of the elimination reactions of 7 and 8.

Preparation of 1-(methyl-1-p-nitrobenzoylperoxyethyl)-cyclohexyl chloride 20:

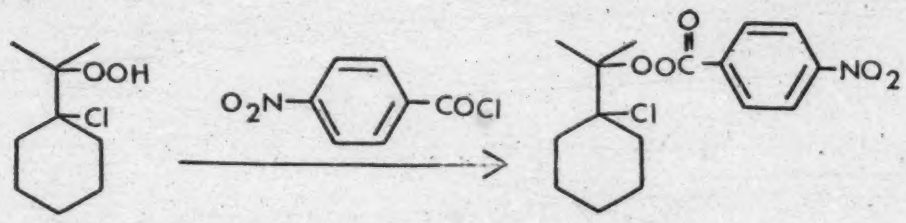
This compound, 20, was prepared to obtain a very pure sample of a β-haloperoxide that could be treated with base to produce allylic hydroperoxides which were not formed from possible impurities in the starting materials. Van de Sande (1) has prepared the corresponding derivative of tetramethylethylene and found that, upon treatment with base, allylic hydroperoxides were formed. This reaction sequence is shown in Scheme V.

SCHEME V



Compound 20 was prepared by a standard procedure for preparing p-nitrobenzoate derivatives of alcohols (52). The formation of 20 is shown in equation [13].

[13]



9 20

The derivative after repeated fractional recrystallizations was a solid that contained 98.5% of the theoretical peroxide content. The structure of 20 was confirmed by its n.m.r. spectrum and microanalysis.

Reaction of 20 with base:

The reaction of 20 with base was carried out in a manner similar to the reaction of 9 with base. The reaction was complete when the heterogeneous reaction mixture became homogeneous.

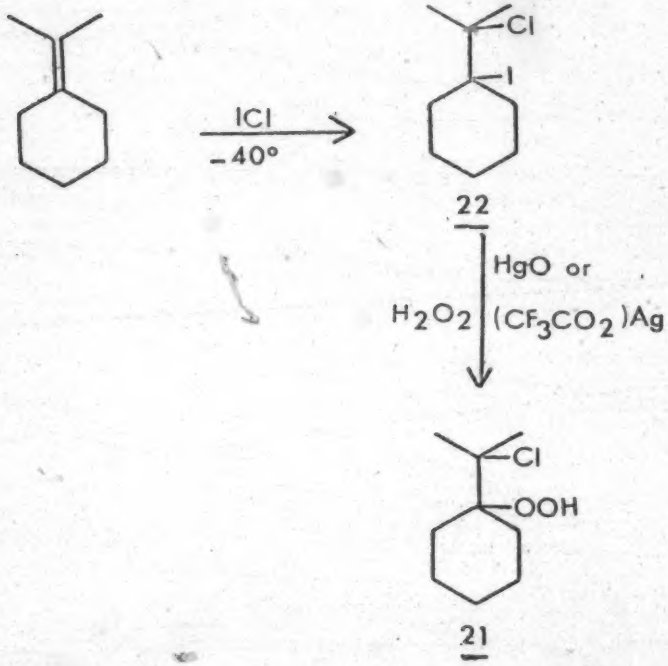
The n.m.r. spectrum of the product mixture showed absorptions characteristic of compounds 16 and 15 in a 16/15 ratio of 13.3. The yield of allylic hydroperoxides was 98%.

Attempted synthesis of 1-(methyl-1-chloromethyl)-cyclohexyl hydroperoxide, 21:

Attempted synthesis of this compound was carried out to determine the product ratio, 16/15, that would be produced by its reaction with base. If the migration of the hydroperoxy group proceeded by way of a perepoxide

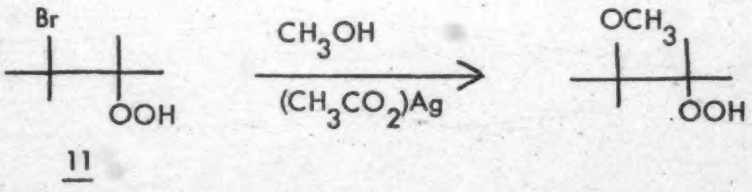
this ratio could be used to determine what fraction of the reaction leading to allylic hydroperoxides had the perepoxide as an intermediate. The synthetic route used in the attempted preparation of 21 is given in Scheme VI.

SCHEME VI



The feasibility of this route lies in the results obtained by Filby (46). He found that treatment of 11 with a methanolic solution of silver acetate gave a product where the bromine was replaced by a molecule of the solvent, shown in equation [14]

[14]



It is known (53) that silver reacts with alkyl iodides much more readily than with alkyl chlorides at low temperatures. Thus, the reaction via the iodochloride may stop at the desired compound 21.

The preparation of the iodochloride, 1-(methyl-1-chloroethyl)-cyclohexyl iodide 22 was accomplished by treatment of the olefin 5 with an equivalent of iodine monochloride at -40°. Because of the instability of this product, it was precipitated from the mother liquor and stored at -78° without recrystallization. Proof of the structure of 22 was obtained by carrying out an elimination reaction on 22 leading to the olefin 5 and by titration of the iodine liberated in this reaction.

1,2-Dihalides are known (54) to undergo elimination reactions leading to the formation of their corresponding olefins in relatively high yields. This has been accomplished by the use of potassium or sodium iodide in acetone. An adaptation of the procedure of Stevens and French (55) was used. When 22 was treated with potassium iodide in acetone, a brown colour instantly appeared and was attributed to the formation of I_3^-. Titration of the I_3^- with a standardized thiosulphate solution showed that 93% of the theoretical amount of iodine had been liberated. The yield of isopropylidenecyclohexane was 82% after work up. The reaction leading to the formation of 5 is shown in equation [15].

[15]

22 5

The titration of I_3^- was carried out slowly so that any iodine absorbed by the acetone could eventually be converted to I_3^- and subsequently titrated.

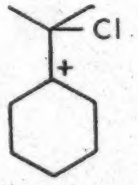
Iodine monochloride has long been known to undergo Markovnikov-type electrophilic addition to ordinary olefins (56, 57). Non-Markovnikov products were reported to increase in yield as the polarity of the solvent was decreased (57). The preparation of the iodochloride of styrene, even in dilute hydrochloric acid, did yield both possible iodochlorides (56). Transformation of a tetrasubstituted olefin to the corresponding iodochloride has not appeared in the literature. The preparation of 22 is the first reported method for preparing a tetrasubstituted iodochloride. As in the case of the preparation of the β-bromohydroperoxide 7, only one product is formed in diethyl ether.

Product analysis of iodochlorides have been generally carried out by analysis for halides, precipitated as silver salts and by elimination reactions yielding the original olefin (56). The titration of the liberated iodine in the analysis of 22 offers an alternate, quick method for the analysis of these types of compounds.

The replacement of the iodine with a hydroperoxy group was first attempted by the addition of one equivalent of silver trifluoroacetate to one equivalent of 22, dissolved in an ethereal solution containing 25% hydrogen peroxide at -40°. The reaction was instantaneous because yellow silver iodide immediately formed upon addition of silver trifluoroacetate. The excess hydrogen peroxide was removed by washing with water.

The n.m.r. spectrum (CCl_4) of the crude product showed absorption at τ4.35, corresponding to the position of the vinylic protons of 16, overlapping singlets at τ8.05, τ8.35, τ8.45, and τ8.75. The singlet at τ8.05 was attributed to the gem-dimethyl groups of 22, while the singlet at τ8.75 was attributed to the gem-dimethyl groups of 16. Low temperature recrystallization from isopentane gave a white, low melting solid with an n.m.r. spectrum identical to 16. If the number of equivalents of silver trifluoroacetate used for this reaction was increased, no starting material could be detected in the n.m.r. spectrum of the product mixture.

The β-chloro carbonium ion, shown below, formed after extraction of iodide by silver was thought to be decomposing. An attempt to trap this intermediate was enhanced by using a solution containing 50% hydrogen peroxide. The temperature was raised to 0° to ensure a homogeneous reaction mixture.



Addition of the iodochloride to the ether solution containing 50% hydrogen peroxide, brought about an immediate decomposition of 22 before addition of the silver salt. Rapid addition of the silver salts was then used to keep decomposition before reaction to a minimum.

The crude product gave absorption in the n.m.r. spectrum (CCl_4), appearing at τ1.8 for the hydroperoxy protons and a large envelope centred at τ8.6 with sharp overlapping singlets at τ8.25, τ8.75 and τ8.6. The area of the hydroperoxy peak at τ1.8 and the area of the remaining peaks were compared and found to be in a ratio of 1:10, while that calculated for the expected product was 1:16. This product was treated with base and the resulting mixture was analyzed for the appearance of 15 and 16. Their production was confirmed by n.m.r. spectroscopy by the appearance of very weak signals at τ5.05 and τ4.35. Because of the high concentration of products containing more than one hydroperoxy group, mercuric oxide was employed to remove the iodine. Mercury was expected to be more selective in the removal of iodine, thus keeping the chlorine on the final product. This reaction was first attempted at -40° in an ether solution composed of 25% hydrogen peroxide. At this temperature no reaction was observed. The solution was allowed to warm to 0° at which time the reaction appeared to commence. Removal of the mercury salts was accomplished by filtration and precipitation from isopentane.

The n.m.r. spectrum (CCl_4), taken after solvent removal, showed a large envelope centred at τ8.5 with many overlapping sharp singlets. The sharp singlet at τ8.05 was attributed to 22 remaining after work up. No product with the predicted n.m.r. spectrum of 21 was obtained from low temperature recrystallization or low temperature chromotography on silica gel. This reaction was repeated with an ether solution composed of 50% hydrogen peroxide at 0°. Again decomposition of the iodochloride was observed before addition of the mercuric oxide. The n.m.r. spectrum (CCl_4) of the product mixture was the same as that obtained from the silver reaction carried out under identical conditions.

The p-nitrobenzoate derivative of 21 formed in either of the mercuric oxide reactions would be expected to be crystalline. This would make possible the purification of any 21 formed in these reactions by recrystallization of its p-nitrobenzoate derivative. No product with the expected n.m.r. spectrum of the p-nitrobenzoate derivative of 21 was found. The n.m.r. spectrum of the product formed upon treatment of the mother liquor with base, showed no signals equivalent to 16 or 15.

This method for the synthesis of 21 was abandoned because of the array of products obtained and the low, inconsistent yields, if any at all, of 21 produced.

Photosensitized oxidation of 5:

In order to gain further insight into the process whereby allylic hydroperoxides are formed from β-halohydroperoxides and triphenyl phosphite ozonide oxidation of olefins, it was decided to compare the product ratio obtained from singlet oxygen oxidation of 5 with that obtained by the other alternate routes.

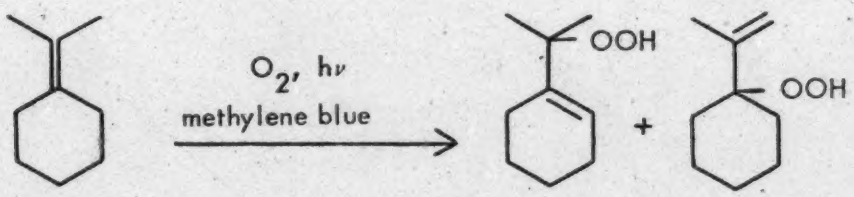
A methanolic solution of 5 was subjected to methylene blue - sensitized photooxygenation. When oxygen uptake had ceased, the solution was poured into water and extracted with ether to remove the dye. The

product mixture after removal of solvent was analyzed for 16 and 15 by n.m.r. spectroscopy.

The n.m.r. spectrum (CCl_4) showed absorption at τ2.3 for the hydroperoxy proton which disappeared upon exchange with deuterium oxide. The absorptions at τ 4.35 and τ 5.05, due to the vinylic protons of the allylic hydroperoxides, gave a 16/15 ratio of 0.11. The remaining absorptions were identical to peaks obtained from pure samples of allylic hydroperoxides.

To prevent any side reactions via a free radical pathway that would ultimately lead to the formation of 15 or 16, a radical scavenger, 2,6-di-t-butylphenol was added to the reaction mixture before irradiation (9). The ratio of allylic hydroperoxides obtained was exactly the same as for the experiment where no free radical inhibitor was added. Thus the allylic hydroperoxides were formed only by the reaction of singlet oxygen with the olefin. The formation of allylic hydroperoxides from the singlet oxygen reaction is shown in equation [16].

[16]



5 16 15

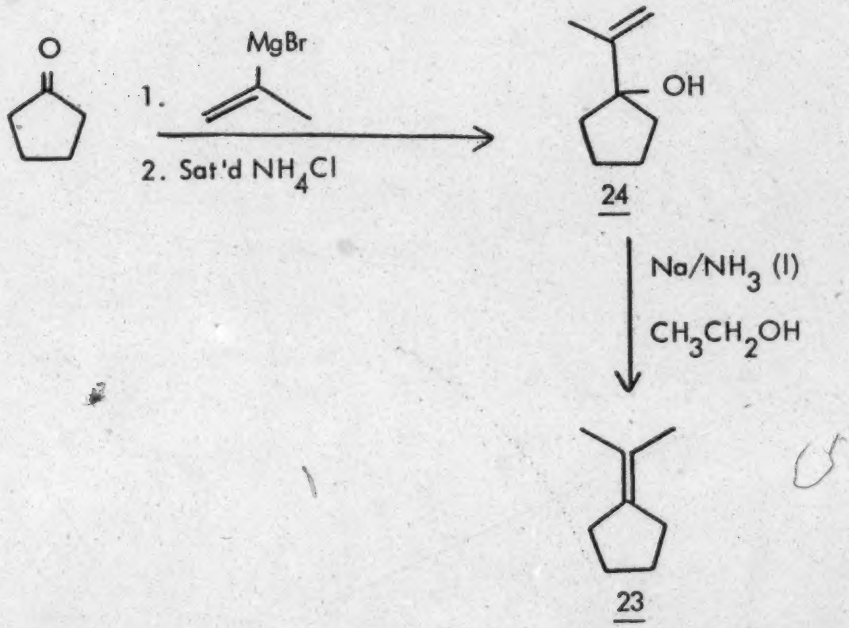
Preparation of isopropylidenecyclopentane, 23:

Isopropylidenecyclopentane was prepared to determine if the hydroperoxy group of its β-halohydroperoxide migrated upon treatment of base to yield allylic hydroperoxides. The singlet oxygen reaction was also carried

out on 23 as a comparative study to the cyclohexyl system.

The synthesis of 23 is outlined in Scheme VII.

SCHEME VII



The overall yield of 23 was 25%. The preparation of the intermediate, 1-(methylvinyl)-cyclopentanol 24 was carried out by reaction of cyclopentanone with the Grignard reagent of 2-bromopropene. The reaction mixture was worked up with saturated ammonium chloride and the acid sensitive intermediate 24 was distilled from neutralized glassware. The yield of 24 was 50% and the structure of 24 was carefully confirmed by its n.m.r. spectrum, infrared spectrum, microanalysis and mass spectrum.

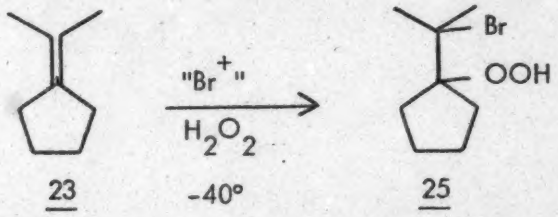
The reduction of 24 was carried out in a manner similar to the reduction of 6 and was converted to 23 in a 50% yield. The structure of 23

was confirmed by comparison of its boiling point, refractive index and infrared spectrum with reported (41) values.

Preparation of 1-(methyl-1-bromoethyl)-cyclopentyl hydroperoxide, 25:

The reaction between 23, one equivalent of 1,3-dibromo-5,5-dimethylhydantoin and a four fold excess of hydrogen peroxide in ether at -40° was accomplished by the method used for the preparation of 7. The peroxide content of the oil obtained after solvent removal was 73% and further purification was not attempted. The assignment of structure was based solely on the n.m.r. spectrum (CCl_4) which showed absorption at τ 8.15 for the gem-dimethyl group, a broad signal at τ8.1 for the ring protons and a singlet at τ 3.35, which disappeared upon exchange with deuterium oxide. The relative positions of the bromine and hydroperoxy groups were determined by comparison with the n.m.r. spectrum of 7 and the β-halohydroperoxides of tetramethylethylene 10, 11, and 12. The formation of 25 is shown in equation [17].

[17]



23 -40° 25

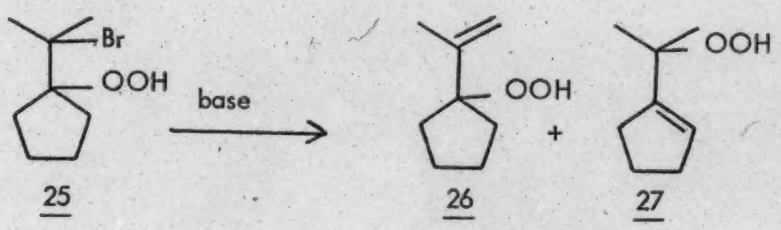
The formation of the bromohydroperoxide 25 was the expected result. Sisti (51) found the treatment of 23 with N-bromosuccinimide and water resulted in the corresponding bromohydrin with the bromine and hydroxy groups in the same positions as found for the bromine and hydroperoxide groups of 25. The forma-

tion of 7 from 5 and 25 from 23 is an example demonstrating the effects of I - strain governing orientation in an electrophilic reaction (51).

Reaction of 25 with base:

The reaction of 25 with base was carried out to determine the extent of hydroperoxy group migration in the formation of allylic hydroperoxides. Preliminary experiments were carried out on impure samples of 25. The expected products from the reaction of 25 with base are shown in equation [18].

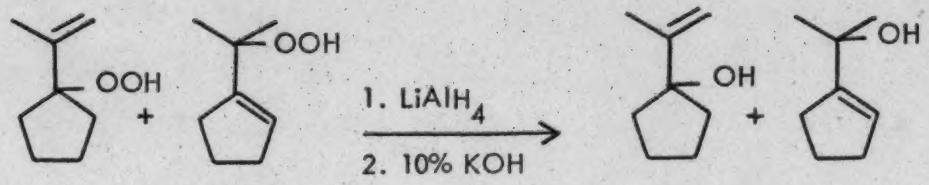
[18]



25 26 27

The vinylic protons used to calculate the 27/26 ratio appeared in the n.m.r. spectrum of the product mixture at τ 4.4 and τ 5.05 for 27 and 26 respectively. The areas of these signals, taking into account that the signal at τ 4.4 was due to two protons, were used to calculate the 27/26 ratio. This ratio was found to be 1.0. To ensure that these vinylic absorptions in the n.m.r. spectrum were not being enhanced by signals due to impurities, an ether solution of this product mixture was treated with $LiAlH_4$. This reaction is shown in equation [19].

[19]



26 27 24 28

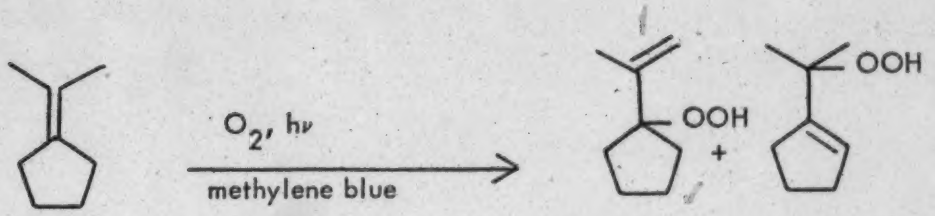
The product mixture was analyzed by n.m.r. spectroscopy and vinylic absorption, equivalent to those found for compound 24, was observed along with vinylic absorption at τ4.5, the expected position for the vinylic absorption due to 28. From the areas of these peaks, the 28/24 ratio was also found to be 1.0.

Photosensitized oxidation of 23:

The dye-sensitized oxidation of 23 was carried out to compare the product distribution of this reaction with that previously obtained under similar conditions for 5. The olefin 23 was subjected to methylene blue - sensitized oxidation under the same conditions used for photooxygenation of 5. It was noted that the theoretical amount of oxygen was consumed at least three times as fast for this reaction as for the reaction of 5 with singlet oxygen.

The n.m.r. spectrum of the product mixture was very similar to the n.m.r. of the product obtained after treating 25 with base. No additional absorptions could be detected. The 27/26 ratio was calculated to be 0.62. The transformation of 23 to allylic hydroperoxides 26 and 27 is shown in equation [20].

[20]



23 26 27

Further experiments with isopropylidenecyclopentane are being conducted in this laboratory by P.A. Lockwood.

Determination of the pKa's of 7, 8, and 9:

When it was originally thought during this project that varying the halogen atom affected the 16/15 ratio, the effect of the halogen atom on the pKa of the hydroperoxy proton was investigated. Richardson (58) correlated the position of the -O-O-H proton absorption in the n.m.r. spectra of some tertiary hydroperoxides recorded in DMSO (d_6) to the pKa's of these molecules. By carrying out various experiments, he arrived at the relationship for the pKa's of tertiary hydroperoxides given in equation [21].

[21] $$pKa = (-0.43 \pm 0.07)\ \delta\ ppm + 17.88 \pm 0.81$$

The position of the hydroperoxy peak in his systems did not vary in solutions of 25% to 10% weight/volume. The conditions of his experiments were used to calculate the pKa's of the tertiary β-halohydroxperoxides 7, 8, and 9. Although the pKa's vary over a range, 13.15 to 14.70, the error involved in this calculation tends to make these results insignificant (Table III): The pKa's of these halohydroperoxides increased with decreasing electronegativity of the halogen atom. This was the expected trend.

TABLE III

Position of the Hydroperoxide Protons in the N.M.R. Spectra of 7, 8 and 9 in DMSO (d_6).

Halohydroperoxide	Solution Composition % weight/volume	Hydroperoxide Proton (ppm.)	pKa	Error (ppm.)
9	6.3	11	13.15	± 1.61
7	7.3	10.5	13.37	± 1.53
8	7.0	7.4	14.70	± 1.32

Rate of reaction of 7 with base:

In experiments producing allylic hydroperoxides by reaction of 7 with base, the reaction was observed to be complete in reaction times less than 1.5 hours. Van de Sande (1) has reported that the half-life ($t_{1/2}$) for the reaction of the bromohydroperoxide of tetramethylethylene was approximately 1 hour, where the concentration of β-bromohydroperoxide was 0.232 M; the concentration of sodium hydroxide was 0.575 M and the solvent used was methanol at -17.5°. This reaction appeared to be faster than the reaction of 7 with base. This was not the expected trend since relief of steric strain in 7 should lead to a $t_{1/2}$ shorter than that found for the bromohydroperoxide of tetramethylethylene. The conditions used to determine the $t_{1/2}$ of the reaction of 7 with base were 0.097 M 7 and 0.160 M sodium hydroxide in 10% water, 90% methanol at 0°.

The half-life was determined by quenching aliquots of the reaction mixture with acetic acid and analyzing the product for disappearance of starting material, 7. The amount consumed could be determined using p-dimethoxybenzene as an internal standard. The reaction was found to be complete after 0.5 minutes.

Rate of reaction of 3-bromo-2,3-dimethyl-2-butyl hydroperoxide, 11, with base:

Because the half-life of the reaction of 7 with base contrasted sharply with the half-life for the reaction of 11 with base, reported by van de Sande (1), an experiment similar to that used for 7 was carried out under the conditions shown in Table IV. The half-life determined by this method was less than 30 seconds. The disappearance of the bromohydroperoxide peaks at τ 8.55 and τ 8.19 (1) were compared to the internal standard, p-dimethoxybenzene, peaks for determination of the half-life of this reaction.

TABLE IV

Rate of Reaction of 3-Bromo-2,3-dimethyl-2-butyl Hydroperoxide 11, [0.0721 M] at 0° with Sodium Hydroxide [0.163 M] in 10% water - 90% Methanol Solution.

Time (seconds)	11 [M]	
30	0.0270	
120	0.0100	
300	0	$t_{1/2} < 30$ seconds
600	0	

DISCUSSION

Mechanism of singlet oxygen oxidation

The photosensitized oxygenation of 5 was initially carried out to provide a comparative reaction for the interpretation of the results found for the formation of allylic hydroperoxides from β-halohydroperoxides and oxidation of alkenes by triphenyl phosphite ozonide. However the results of this experiment also led to a better understanding of the mechanism involved in the singlet oxygen reaction.

The most widely accepted mechanism for this transformation is the concerted mechanism which has been discussed in the introduction. Klein and Rojahn (22) found no oxygenation products from the singlet oxygen reaction with methylenecyclohexane and metheylenecyclopentane. Gollnick (59), on studying the photooxygenation products of 1-methylcyclohexene and 1,2-dimethylcyclohexene, concluded that the abstraction of a methyl hydrogen was thermodynamically more favourable than abstraction of a quasi-axial or quasi-equatorial hydrogen. From these two results we expected that the product obtained on photooxygenation of 5 would be exclusively 15. In fact, substantial amounts of 16 were formed in this reaction. The formation of 16 via a free radical pathway is not possible. The product distributions from reactions with and without a free radical inhibitor were identical. Thus, these two allylic hydroperoxides must arise from attack of singlet oxygen on the olefin.

The conclusion of Klein and Rojahn, that the distance between the vinyl carbon and the axial or quasi-axial hydrogen is too large to form a cyclic transition state, does not hold for 5. The same result was found in the photooxygenation of 23. Compounds containing quasi-axial hydrogens have recently been photooxygenated to produce allylic hydroperoxides (60). Cyclohexylidenecyclohexane and cyclopentylidenecyclopentane, containing allylic

hydrogen in the same conformation as the allylic hydrogen in methylenecyclohexane and methylenecyclopentane have been photooxygenated to produce allylic hydroperoxides (60). This result confirms our observations.

Sharp (4) and Kopecky (5) found that tetrasubstituted olefins reacted much faster than disubstituted olefins. The tetrasubstituted exocyclic double bond of 23 was found to react at least three times faster than the tetrasubstituted exocyclic double bond of 5. This faster rate that was observed for the photooxygenation of cyclopentyl exocyclic double bond over the cyclohexyl analogue, has been confirmed by the results reported recently (60). It was found that photooxygenation of cyclopentylidenecyclopentane was much faster than the photooxygenation of cyclohexylidenecyclohexane. These results indicate that the slower the rate of photooxygenation of an olefin, the more regioselective is the hydrogen abstraction. Thus, no products are produced in the photooxygenation of methylenecyclohexane and methylenecyclopentane, while the photooxidation of 5 and 23 produced product ratios of 0.11 and 0.62 respectively. The concerted mechanism had been originally proposed to explain the geometric requirements of the photooxygenation reactions; however these requirements seem to decrease with increasing reactivity of the double bond.

The intermediacy of a perepoxide cannot explain the stereochemistry observed in the products of these reactions. If it were so, the product distribution would more closely resemble that found for the reaction of the corresponding β-halohydroperoxides. In fact, the product distributions are very different and will be discussed further. However, Schaap (61) has reported the trapping of the perepoxide intermediate in the photooxygenation of adamantylideneadamantane. It should be noted, however, that this is a special case of the dye-sensitized photooxygenation because no allylic hydroperoxides have been reported to be formed in this reaction.

Oxygenation by triphenyl phosphite ozonide

Only one product was observed on oxidation of 5 by triphenyl phosphite ozonide at -78°. This is a variation from the product mixture obtained in the singlet oxygen reaction of 5. Van de Sande (1) has shown that the product distribution obtained upon photooxidation of 2,3-bis-(trideuteriomethyl)-2-butene did not vary with temperature. Thus the comparison of the product distribution from these two methods can be made even though different reaction temperatures were used. It has been shown that singlet oxygen does not intervene in the triphenylphosphite ozonide oxidation at low temperatures (40). The results here also indicate that singlet oxygen is not an intermediate in this reaction. The reaction with singlet oxygen is not a diffusion controlled reaction (62) so that a significant amount of singlet oxygen, if formed on the decomposition of the ozonide, equation [22],

[22]

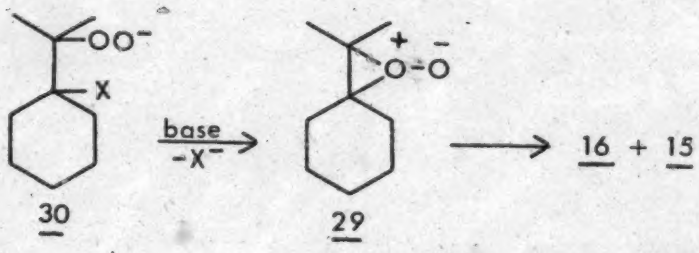
$$(\phi O)_3PO_3 \longrightarrow {}^1O_2 + (\phi O)_3PO$$

would be deactivated before it could react with the olefin. This would result in non-quantitative reaction between equal equivalents of the ozonide and 5. In fact, this reaction was found to be quantitative. Another pathway is required for oxygenation by this procedure.

Conversion of halohydroperoxides to allylic hydroperoxides

The production of 15 in the reaction of 7, 8, and 9 with base and the production of 27 by treatment of 25 with base, shows that a migration of the hydroperoxy group takes place. The only plausible route for this migration is that the formation of 15 from 7, 8 and 9 proceeds by way of a perepoxide intermediate 29, equation [23].

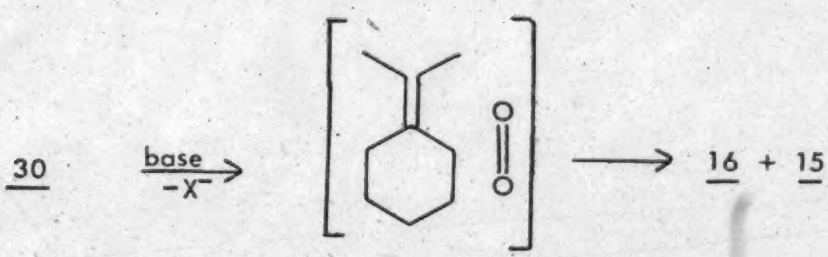
[23]



30 29

This migration could not have occurred by fragmentation of the anion 30 to give the alkene 5, singlet oxygen and halide ion followed by reaction between 5 and singlet oxygen, equation [24].

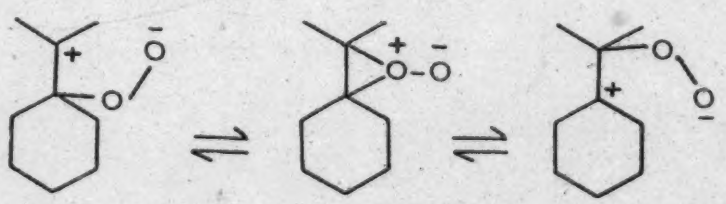
[24]



This route was ruled out on two grounds. First, the reaction should not have been quantitative because the reaction of an olefin with singlet oxygen is not diffusion controlled (62). In fact, this reaction was found to be quantitative. Second, the distribution of products should have been the same as obtained from the photooxygenation of 5. In fact, they were not.

The migration of the hydroperoxy group in the present system could be formulated as proceeding by way of a pair of rapidly interconverting, open chain zwitterions, equation [25].

[25]



Evidence that such open chain zwiterrions do not play a role in the conversion of halohydroperoxides to allylic hydroperoxides has been reported (1). The

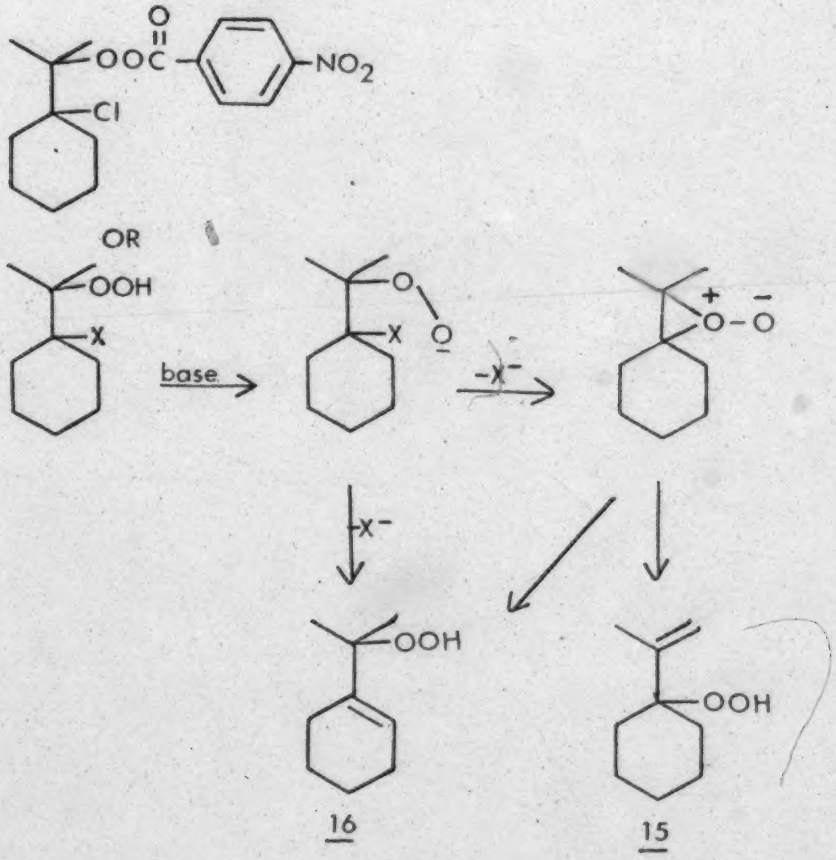
present system does not offer evidence for or against such a pathway.

Intervention of 1,2-dioxetanes as intermediates in the conversion of alkenes to allylic hydroperoxides via treatment of β-halohydroperoxides with base can be disregarded as a general phenomenon as it has been shown that trimethyl - and tetramethyl-1,2-dioxetane are not converted to allylic hydroperoxides even when treated with base. This appears to leave as a result of this process of elimination, formation and subsequent reorganization of the perepoxide as the pathway for migration of the hydroperoxy group. Under the reaction conditions used, 29 could be converted to 15 either by an intramolecular reorganization or by reaction with base.

Because the reaction of the p-nitrobenzoate derivative 20 of 9 gave the same product distribution as the reaction of 9 with base, the intermediate leading to hydroperoxy group migration must be identical. Also the observation that the three different halogen atoms had no effect on the product distribution, tends to rule out the possibility of a direct elimination of HX as a competing pathway to the formation of 16. However, this argument is not conclusive so that formation of allylic hydroperoxides, either from direct elimination of HX or from the perepoxide intermediate 29 must be considered, Scheme VIII.

Direct elimination of HX would form the product with the most stable double bond as would the rearrangement of the perepoxide intermediate. Similar arguments can be made to account for the migration of the hydroperoxy group when 25 was treated with base to yield substantial amounts of 27. This increase in the amount of migration product compared to that found in the cyclohexyl system is an argument against a direct elimination of HX yielding some of the non-migration product. The thermodynamically more stable double bond is found to form in increasing yields for this reaction to a point where 27 is the major product (63). Thus, the formation of 26 by a direct elimination reaction becomes at most, a minor competing pathway.

SCHEME VIII

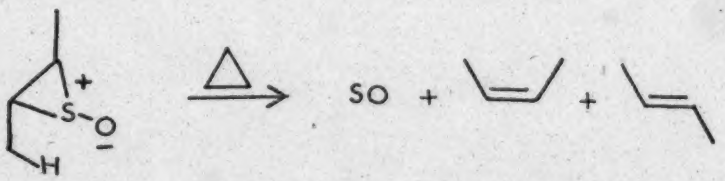


There are now reported compounds which have structures and give reactions analogous to the perepoxide 29. Baldwin (64, 65) has reported two of these classes of strained dipolar species. The first, an episulphoxide (64) when suitably substituted, rearranges thermally to give an allylic sulphenic acid, equation [26].

[26]

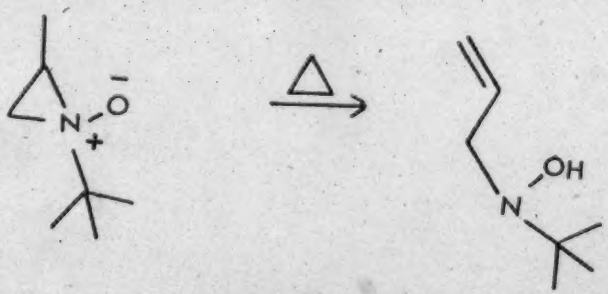
However, when there are no hydrogens available for abstraction or when the temperature of the reaction is increased, these episulphoxides have been shown to decompose via a free radical mechanism to sulphur monoxide and the corresponding olefin (64, 66), equation [27].

[27]

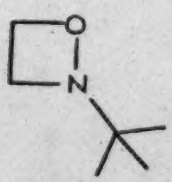


The second class of compounds, aziridine N-oxides (65), also when suitably substituted, thermally rearrange to give allylic hydroxylamines, equation [28].

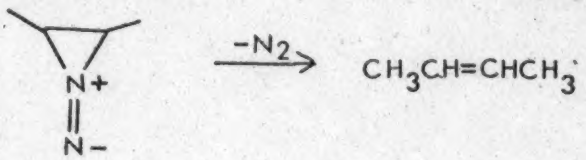
[28]



This product has been shown to be produced via an intermediate other than a 1,2-oxazetidine, shown below, an analagous compound to the 1,2-dioxetanes.

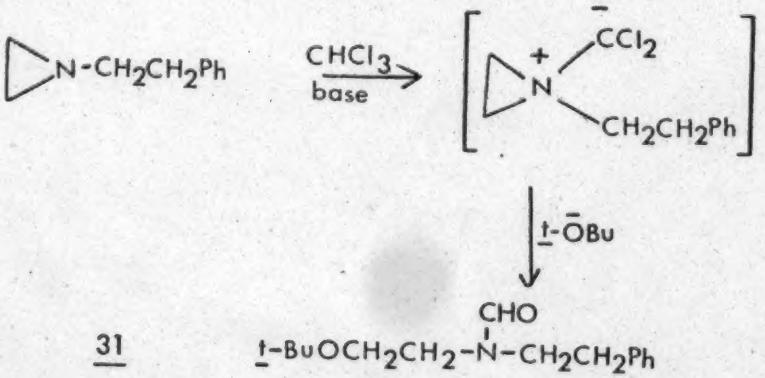


Other compounds and proposed reaction intermediates have appeared in the literature which also have analagous structures to the perepoxide. One such intermediate is shown in equation [29].

[29] 

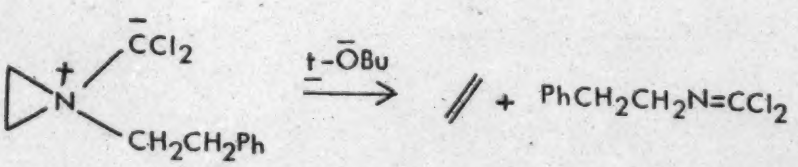
This intermediate decomposes to form the olefin with the elimination of nitrogen (67, 68).

In the reaction of N-phenethylaziridine with chloroform in the presence of potassium t-butoxide, an intermediate with an analogous structure to a perepoxide has been proposed (69). This intermediate may rearrange in a similar fashion to yield a compound having the structure 31, equation [30].

[30] 

31 $t\text{-BuOCH}_2\text{CH}_2\text{-N(CHO)-CH}_2\text{CH}_2\text{Ph}$

This intermediate may also lead to fragmentation products (6), equation [31].

[31] 

Thus it can be seen that the proposed intermediate 29 has analogies in the literature and its proposed structure and rearrangement reaction is not unfounded.

The half-life ($t_{1/2}$) of the reaction of 11 with base is in direct contrast with the half-life of the reaction determined by van de Sande (1). The $t_{1/2}$ for the reaction of 7 with base was expected to be shorter than the $t_{1/2}$ for the reaction of 11 with base. This, in fact, was the observed result, but the half-life of the reaction of 7 with base was so short that exact comparison was not possible. The shorter half-life of the reaction of 7 with base than the reaction of 11 with base may arise from the following reasons. A bromine in the axial position has less 1,3-diaxial repulsions than does an isopropyl group (7). Thus the conformation of the cyclohexyl ring would be such that the bromine would be in the axial position. This would facilitate the direct elimination reaction. Also, loss of the bromine by whichever mechanism would relieve the 1,3-diaxial interactions, however small they may be. These arguments could account for the shorter $t_{1/2}$ observed in the reaction of 7 with base than the $t_{1/2}$ for the reaction of 11.

It is now evident that the reaction of β-halohydroperoxides with base may be useful in synthetic chemistry. This reaction can, in some cases, be employed to synthesize allylic hydroperoxides that are not formed or that are formed in low yields in the singlet oxygen reaction or the reaction incorporating triphenyl phosphite ozonide as the oxidizing agent.

The observed formation of only one allylic hydroperoxide in the triphenyl phosphite ozonide reaction may lead to the use of this reaction as a synthetic method. The singlet oxygen reaction had been useful for the synthesis of allylic hydroperoxides (71, 72, 73) and where applicable, gave regioselective products due to the geometric requirements already outlined (74, 75, 76). It is now evident that for more reactive olefins, the singlet oxygen reaction is not entirely regioselective and can lead to a mixture of products. Thus, it may be more useful to use the triphenyl phosphite ozonide

reaction, rather than the singlet oxygen reaction to synthesize regiospecific allylic hydroperoxides.

EXPERIMENTAL

Physical measurements:

All melting points and boiling points are uncorrected. Melting points were taken on a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 421 Grating Spectrophotometer. Nuclear magnetic resonance (n.m.r.) spectra were obtained on a Varian Analytical Spectrometer, Model A-60, using tetramethylsilane as internal reference. The following abbreviations were used: (s) = singlet; (b) = broad signal; (d) = doublet; (m) = multiplet; (q) = quartet; J = coupling constant. Refractive indices (n_D) were taken on a Bausch and Lomb Abbe - 3L Refractometer. Mass spectra were recorded on an AEI Model MS - 2 Spectrometer. Spectra were recorded in the following fashion: m/e: peak mass.

Purification of materials:

Tetrahydrofuran (THF):

Commercial THF was distilled twice from lithium aluminum hydride ($LiAlH_4$) through a vigreux column immediately before use.

2-Bromopropene:

2-Bromopropene was used as supplied by the Columbia Chemical Company. Yields for Grignard reagents prepared from 2-bromopropene are based on magnesium.

3-Bromo-2, 3-dimethyl-2-butyl hydroperoxide, 11:

A crude sample of this material was donated by R. Sawka and recrystallized three times from Skelly B.

Neutralization of apparatus:

All pieces of apparatus used to distill compounds 6, 14, 17, and

24 were carefully neutralized. After treatment overnight in a chromic acid bath, the glassware was washed with distilled water, then immersed in concentrated ammonia for several hours. The ammonia was washed off with distilled water and finally, the apparatus was baked out at 130° overnight.

Solvent removal:

Solvent removal was carried out at a reduced pressure on a rotary evaporator.

Yield calculations:

Yields of compounds 16 and 15 were determined by n.m.r. spectroscopy as outlined in the results section. A weighed sample of the internal standard was initially added to the reaction mixtures.

The 16/15 ratios and the 27/26 ratios were determined on the basis of n.m.r. spectroscopy. This procedure was also outlined in the results section.

Hydroperoxides:

All preparations and reactions of hydroperoxides were carried out behind shields. At no time during this work did an explosion occur, but rapid decomposition of the iodohydroperoxide did occur at room temperature. All peroxide containing compounds were stored in dry ice. Hydroperoxide content was measured iodemetrically, using the procedure of Organic Synthesis (77).

1-(Methylvinyl) - cyclohexanol, 6:

A Gignard reagent was prepared by a known procedure (45). In a 3-necked flask equipped with reflux condenser, dropping funnel and mechanical stirrer, was added a mixture of a few ml. of 2-bromopropene, 12.2 g. (0.5 mole) magnesium turnings and 400 ml. THF. Once the reaction had

started, a total of 60.5 g. (0.5 mole) 2-bromopropene dissolved in 150 ml. THF was added dropwise.

After the solution was stirred and held at reflux for 15 minutes, 49 g. (0.5 mole) cyclohexanone in 40 ml. THF was added slowly. The mixture was refluxed for a further 15 minutes and then the solution was treated with saturated ammonium chloride until the solution became clear. The ether layer was removed and the residue was extracted with ether (3 x 100 ml.). The combined ether and THF portions were washed with water (3 x 100 ml.), dried ($MgSO_4$) and concentrated to leave an oil which was distilled, giving 46.2 g. (66%) of allylic alcohol 6, b.p. 54° (2.5 mm.), n_D^{25} 1.4824.

The infrared spectrum (neat) showed absorption at 3450 (O-H stretch) and 1635 (C=C stretch).

The n.m.r. spectrum (CCl_4) showed absorption at τ5.05 (s), τ5.2(s), τ7.95 (s) (which disappeared upon exchange with deuterium oxide), τ 8.2 (d, J = 1 cps), τ8.45 (b) in the ratio 1:1:1:12, required 1:1:1:12. The areas of the aliphatic protons were combined.

Analysis: Calculated for $C_9H_{16}O$: C,77.14; H,11.42. Found: C,77.13; H,11.41.

Isopropylidenecyclohexane, 5:

This reduction procedure was adapted from the one described by Birch (44). A solution of 28 g. (0.2 mole) 6 and 10 g. ethanol dissolved in 50 ml. ether was added to a solution of 10 g. (0.4 mole) sodium in 270 ml. liquid ammonia. A further 10 g. ethanol was added and the solution was allowed to reflux for 2 hours. Just enough water was cautiously added until decolourization of the solution was obtained. The ammonia was allowed to evaporate overnight.

An additional 100 ml. water was added and the resulting mixture was extracted with ether (3 x 100 ml.). The ether extracts were washed with water until neutral, dried ($MgSO_4$) and concentrated to yield an oil which,

upon distillation gave 17.9 g. (72%) of the olefin 5, b.p. 51-53° (14 mm.), n_D^{20} 1.4710. Reported (41) b.p. 46-48° (13 mm.), n_D^{20} 1.4714.

The infrared spectrum (neat) showed absorption at 1440, 1230 and 2920 as in the reported (41) spectrum.

The n.m.r. spectrum (CCl_4) showed absorption at τ 7.9 (b), τ 8.35 (s) and τ 8.5 (b), ratio 1:3.1, required 1:3.

1-(Methyl-1-hydroperoxyethyl)-cyclohexyl bromide, 7:

This bromohydroperoxide was prepared by an adaptation of a procedure described by Mumford (30). To 60 ml. ether stirred at -40°, 17.0 g. (0.5 mole) 98% hydrogen peroxide was added in small portions. The additions were made at such a rate that the temperature did not rise above -30°. On reattaining -40°, 12.4 g. (0.1 mole) 5 was added in one portion. Then 14.5 g. (0.05 mole) 1,3-dibromo-5,5-dimethylhydantoin was added and the solution was stirred for an additional 30 minutes. The cooling bath was removed and its contents were allowed to warm to ca. 10°. When the mixture had become homogeneous it was cautiously poured into 50 ml. water. The organic layer was separated, washed with water (4 x 50 ml.), washed with 10% sodium thiosulphate until colourless, dried ($MgSO_4$) and concentrated. The crude product, 29.7 g. of an oil, contained 76% of the theoretical hydroperoxide as determined by iodometric titration. The crude material was recrystallized from Skelly B (3x) yielding a white solid, m.p. 55-56°, containing 99.7% theoretical hydroperoxide.

The n.m.r. spectrum ($CDCl_3$) showed absorption at τ 3.0 (b) (which disappeared upon exchange with deuterium oxide), τ 8.3 (b) and τ 8.5 (s), ratio 1:9.6:5.5, required 1:10:6.

The mass spectrum gave peaks at m/e: 219 (P-18), 203 (P-34) and 123 (P-114).

Dimethylcyclohexyl carbinol, 14:

In a 3-necked flask fitted with a mechanical stirrer, dropping funnel and reflux condenser, a Grignard reagent was prepared in the usual manner from 13.5 g. (0.55 mole) cyclohexyl bromide, and 225 ml. ether. To this solution was added 29 g. (0.5 mole) acetone dissolved in 150 ml. ether.

The resulting mixture was hydrolyzed with saturated ammonium chloride solution. The solid residue was extracted several times with fresh ether. The ether was removed and the residue distilled to yield 20.9 g. (31%) of alcohol 14, b.p. 80-84° (10 mm.), n_D^{24} 1.4660. Reported (78) b.p. 85-86° (14 mm.), n_D^{25} 1.4656.

The n.m.r. spectrum ($CDCl_3$) showed absorption at τ8.2 (b), τ8.9 (s) and τ8.7 (s) (which disappeared upon exchange with deuterium oxide), ratio 16:1, required 17:1. The areas of the aliphatic protons were combined.

The infrared spectrum (neat) showed absorption at 3360 (O-H stretch).

Determination of the structure of 7:

Reduction of 7:

This compound was reduced by a general procedure outlined by Davies and Feld (47) and modified by Filby (46) for bromohydroperoxides. To a solution of 2.62 g. (0.01 mole) triphenylphosphine in 50 ml. Skelly B was added 2.37 (0.01 mole) 7 in 10 ml. Skelly B. The reaction mixture was stirred for an additional hour and subsequently filtered. The mother liquor was shaken with 30% hydrogen peroxide (30 ml.), filtered, washed with water (3 x 25 ml.) and concentrated. The residue was then eluted through a silica gel column (ca. 5 cm. x 20 cm.) with ether (25%)/Skelly B to yield 2 g. (90%) of an oil, 1-(methyl-1-hydroxyethyl)-cyclohexyl bromide, 13.

The n.m.r. spectrum (CCl_4) showed absorption at τ7.95 (s) (which disappeared upon exchange with deuterium oxide), τ 8.35 (b) and τ8.70 (s), ratio 1:17, required 1:16. The areas of the signals at τ8.35 and τ8.70 were

combined.

Debromination of 13:

An adaptation of the procedure of House (49) was used to carry out the debromination. To a solution of 2 g. (0.009 mole) 13 in 30 ml. benzene was added 2.9 g. (0 01 mole) tri-n-butyltin hydride (48). The solution was allowed to stir at reflux temperature for an additional 12 hours. The solution was concentrated to yield an oil which was chromatographed on a silica gel column (ca. 5 cm. x 35 cm.) by eluting with Skelly B/ether to yield 1 g. (87%) 14.

The infrared spectrum (neat) showed absorption at 3360 (O-H stretch).

The n.m.r. spectrum ($CDCl_3$) showed absorption at τ8.2 (b) and τ8.9(s). The areas of these overlapping peaks decreased on exchange with deuterium oxide. The n.m.r. spectrum was the same as the n.m.r. spectrum of previously prepared 14.

1-(Methylvinyl)-cyclohexyl hydroperoxide, 15:

This oxidation procedure was adapted from that described by Bartlett and Mendenhall (40). A 100 ml. flask containing 40 ml. methylene chloride was cooled to -78° and this temperature was kept constant during the entire reaction. A stream of oxygen carrying ozone was then continuously bubbled through the solution. The blue ozone colour was maintained while 3.1 g. (0.01 mole) triphenyl phosphite dissolved in 10 ml. methylene chloride was slowly added. Nitrogen was then bubbled through the solution until the mixture became colourless. Finally, 1.2 g. (0.01 mole) 5 was added in one portion. The solution was allowed to stand under a nitrogen atmosphere for an additional 12 hours after which time it was allowed to warm to room temperature and then concentrated to yield 15 virtually quantitatively, as determined by n.m.r. spectroscopy. To this residue was added 50 ml. isopentane and the resulting mixture was filtered. The mother liquor was concentrated and the resulting residue was chromotographed on silica gel (ca. 2 cm. x 25 cm.) by elution with Skelly B/ether at -40°. The fractions having peroxide content

were dissolved in isopentane and cooled to -78°. The mother liquor was decanted from crystals that formed. This procedure was repeated several times to finally yield a white solid, m.p. 17-19°, containing 99.5% theoretical peroxide.

The n.m.r. spectrum (CCl_4) showed absorption at τ 2.6 (s) (which disappeared upon exchange with deuterium oxide), τ 5.05 (s), τ 8.25 (d, J = 1 cps) and τ 8.5 (b), ratio 1:2:13.5, required 1:2:13. The areas of the signals at τ 8.25 and τ 8.5 were combined.

Reduction of 15:

An adaptation of the reduction procedure described by van de Sande (1) was used. To a solution of 1.2 g. (0.03 mole) lithium aluminum hydride ($LiAlH_4$) in 80 ml. ether, in a 250 ml. 3-necked flask, fitted with reflux condenser, dropping funnel, stirrer and ice-bath, was added 0.78 g. (0.005 mole) 15 in 10 ml. ether. After addition was complete the ice-bath was removed and the solution was heated to reflux for 2 hours. A 10% potassium hydroxide solution was added slowly with stirring until the ether solution became clear. The ether was decanted from the solid residue and the residue was extracted with ether (3 x 50 ml.). The combined ether extracts were concentrated to yield 0.66 g. (94%) of allylic alcohol 6.

The infrared and n.m.r. spectra of 6 were identical to those of the product 6, prepared via the Gignard reagent as described previously.

1-Acetylcyclohexene, 18:

This was prepared according to the method of Royals and Hendry (79). A mixture of 123 g. (1.5 moles) cyclohexene and 260.5 g. (1.0 mole) anhydrous stannic chloride was place in a 1-l., 3-necked flask fitted with dropping funnel, thermometer and mechanical stirrer. The flask was immersed in an ice-bath and 102 g. (1.0 mole) acetic anhydride was added dropwise over 30 minutes; the temperature varied between 25-35°. Stirring was contin-

ued for an additional 15 minutes. The mixture was extracted with ether (3 x 100 ml.). The combined ether portions were washed with aqueous sodium bicarbonate solution until no gas was evolved, washed with water (100 ml.), dried ($CaCl_2$) and concentrated. The resulting oil was distilled to yield 67 g. (54%) of the ketone, b.p. 64-67° (5 mm.), n_D^{22} 1.4877. Reported (79) b.p. 65-69° (5 mm.), n_D^{20} 1.4881.

The n.m.r. spectrum (CCl_4) showed absorption at τ3.1 (b), τ7.8 (b) and τ8.4 (m), ratio 1:7:4.2, required 1:7:4.

1-(Methyl-1-hydroxyethyl)-cyclohexene, 17:

In a 100 ml., 3-necked flask fitted with reflux condenser, dropping funnel and stirrer, a Grignard reagent was prepared from 1.2 g. (0.05 mole) magnesium turnings, 5 g. (0.051 mole) methyl bromide and 40 ml. ether. To this reagent was added 6.2 g. (0.05 mole) 18 dissolved in 10 ml. ether. After refluxing for an additional 15 minutes, the reaction mixture was treated in the usual fashion with saturated ammonium chloride solution. The residue was extracted with ether (3 x 25 ml.). The combined ether portions were washed with water (25 ml.), dried ($MgSO_4$) and concentrated. The oil was distilled, yielding 4.3 g. (62%) allylic alcohol, b.p. 85-87° (14 mm.), n_D^{28} 1.4812.

The infrared spectrum (neat) showed absorption at 3400 (O-H stretch) and 1640 (weak C=C stretch).

The n.m.r. spectrum (CCl_4) showed absorption at τ4.3 (m), τ7.5 (s) (which disappeared upon exchange with deuterium oxide), τ8.05 (b), τ8.45 (b) and τ8.75 (s), ratio 1:1:8:6, required 1:1:8:6. The areas of the signals at τ8.45 and τ8.05 were combined.

Analysis: Calculated for $C_9H_{16}O$; C,77.14; H,11.42. Found: C,76.28; H,11.62. The mass spectrum gave a peak at m/e: 140 (P).

1-(Methyl-1-hydroperoxyethyl)-cyclohexene, 16:

This reaction was carried out by a procedure adapted from Mumford (3). To a solution of 2.37 g. (0.01 mole) 7 in 60 ml. methanol at 0°, was slowly added 0.44 g. (0.011 mole) sodium hydroxide dissolved in 1 ml. water and 3 ml. methanol, dropwise with stirring. The reaction mixture was allowed to stir at 0° for an additional 20 minutes and then poured into a mixture of 10 ml. water and 10 ml. methylene chloride. The organic layer was removed and the aqueous layer was extracted with methylene chloride (3 x 10 ml.). The combined methylene chloride portions were washed with water (10 ml.), dried ($MgSO_4$) and concentrated to yield 1.5 g. allylic hydroperoxides in a 94% yield, as determined by n.m.r. spectroscopy. The oil was precipitated as a solid several times at -78° from isopentane to yield a white solid m.p. 24-26°, which contained 99.7% theoretical peroxide.

The n.m.r spectrum (CCl_4) showed absorption at τ 2.5 (s) (which disappeared upon exchange with deuterium oxide), τ 4.35 (m), τ 8.0 (b), τ 8.4 (b) and τ 8.75 (s), ratio 1:1:4.2:4.2:5.4, required 1:1:4:4:6.

Reduction of 16:

A solution of 1.2 g. (0.03 mole) $LiAlH_4$ in 80 ml. ether was employed to reduce 0.78 g. (0.005 mole) 16 in 10 ml. ether by the method used for the reduction of 15. The reaction mixture was worked up in the usual fashion to yield 0.69 g. (99%) of allylic alcohol, 17.

The infrared and n.m.r. spectra of 17 were identical to those of the product 17 prepared from 18 as previously described.

1-(Methyl-1-hydroperoxyethyl)-cyclohexyl iodide, 8:

The procedure described for the preparation of the bromohydroperoxide, 7, was used to prepare a sample of 8 from 12.4 g. (0.1 mole) 5, 10.0 g. (0.05 mole) 1,3-diiodo-5,5-dimethylhydantoin, and 17.0 g. (0.5 mole), 98% hydrogen peroxide, in 60 ml. ether. The yellow solid obtained, 35 g., had 67% of the theoretical hydroperoxide content. The crude material

was recrystallized from Skelly B yielding a white solid, m.p. 43° (decomposition) containing 98% theoretical peroxide content. This compound, 8, was unstable at room temperature.

The n.m.r. spectrum (CCl_4) showed absorption at τ 2.7 (s) (which disappeared upon exchange with deuterium oxide), τ 8.2 (b) and τ 8.4 (s), ratio 1:15.7, required 1:16. The areas of the aliphatic peaks were combined.

1-(Methyl-1-hydroperoxyethyl)-cyclohexyl chloride, 9:

The procedure described for the preparation of the iodohydroperoxide, 8, was used with some modification, to prepare a sample of 8 from 1.24 g. (0.01 mole) 5, 0.9 g. (0.005 mole) 1,3-dichloro-5,5-dimethylhydantoin and 9 ml., 98% hydrogen peroxide in 30 ml. ether. The reaction mixture was stirred for an additional 1.5 hours at -30°. The oil obtained, 2.1 g. was added to 10 ml. of isopentane and the resulting mixture was filtered. The mother liquor was cooled to -78° and the resulting crystals were recrystallized several times from isopentane at -78° to yield 0.5 g. (26%) of a white solid, m.p. 46-46.5°, containing 100% theoretical hydroperoxide.

The n.m.r.spectrum (CCl_4) showed absorption at τ 2.5 (s) (which disappeared upon exchange with deuterium oxide), τ 8.1 (b), τ 8.3 (b) and τ 8.6 (s), ratio 1:15.1, required 1:16. The areas of the aliphatic protons were combined.

The mass spectrum gave peaks at m/e: 159 (P-33), and 123 (P-69).

1-(Methyl-1-p-nitrobenzoylperoxyethyl)-cyclohexyl chloride, 20:

The general procedure for the preparation of p-nitrobenzoate esters of alcohols (52) was adapted for compound 20. To a solution of 0.5 g (0.0026 mole) 9, dissolved in 3 ml. anhydrous pyridine was added 0.5 g. (0.0026 mole) p-nitrobenzoyl chloride. The reaction mixture was stirred for an additional 15 minutes and poured with vigorous stirring into 10 ml. water. The precipitate was allowed to settle, and the supernatant liquid was decanted. The

residue was stirred thoroughly with aqueous 5% sodium carbonate (2 x 100 ml.), filtered and recrystallized from Skelly B to yield 0.27 g. (30%) of a solid m.p. 102° (decomposition) containing 98.5% theoretical peroxide.

The n.m.r. spectrum ($CDCl_3$) showed absorption at τ1.6 (A_2B_2 system centred at τ1.6, J = 8 cps), τ8.2 (b) and τ8.4 (s), ratio 1:3.0, required, 1:4.0. The areas of the aliphatic signals were combined and the areas of the aromatic signals were combined.

Analysis: Calculated for $C_{16}H_{20}O_5NCl$: C, 56.23; H, 5.90, N, 4.10; Cl, 10.37. Found: C, 56.04; H, 6.00; N, 4.66; Cl, 10.59.

Reaction of 7 with base:

The reaction of 7 with base was carried out by a procedure similar to that used in the synthesis of 16. Several reactions of 7 with base at 0° were carried out varying concentrations of 7, solvent system, base concentration and the base used. A general method for reaction of 7 with base was as follows. To solution of 2.37 g. (0.01 mole) 7 in 6 ml. methanol at 0° was added 0.60 g. (0.011 mole) sodium methoxide in 4 ml. methanol, dropwise with stirring. The reaction mixture was stirred at 0° for 1.5 hours. The general work up scheme for the reaction of halohydroperoxides with base was as follows. The solution was poured into a mixture of 10 ml. water and 10 ml. methylene chloride. The organic layer was separated and the aqueous layer extracted with methylene chloride (3 x 10 ml.). The combined methylene chloride portions were washed with water (10 ml.), dried ($MgSO_4$) and concentrated. Yields of allylic hydroperoxides determined by n.m.r. spectroscopy, ratio of 16/15 determined by n.m.r. spectroscopy and reaction conditions are given in Table I. Runs 1 - 5 were carried out using crude samples of 7. Runs 6 - 9 were carried out using freshly recrystallized samples of 7. The analysis of the n.m.r. spectra of the products obtained in each experiment was given in the preceding results section.

Reactions of 8 with base:

The reaction of 8 with base at 0° was carried out using the method outlined above. Results of experiments involving reaction of 8 and base at 0° are given in Table II along with the results of the reaction carried out at -40° in the following manner. To a solution of 0.14 g. (5×10^{-4} mole) 8 in 40 ml. methanol at -40° was added 0.063 g. (15×10^{-4} mole) sodium hydroxide in 5 ml. water and 5 ml. water. Addition was such that the temperature was kept constant at -40°. After stirring at -40° for 4 hours, 0.03 g. (15×10^{-4}) mole acetic acid was added and the mixture was allowed tc warm to room temperature. The mixture was then worked up in the usual fashion.

The n.m.r. spectra of the products obtained in runs 1 - 4 were given in the preceding text. Yields of allylic hydroperoxides, 16 and 15 were determined by n.m.r. spectroscopy as was the ratio 16/15. All runs were carried out on recrystallized samples of 8.

Reaction of 9 with base:

The reaction of 9 with base was carried out as previously described at 0°. The yield of 15 and 16 was greater than 98%, as determined by n.m.r. spectroscopy. The 16/15 ratio was also found by n.m.r. spectroscopy. The n.m.r. spectrum of the product was given in the preceding results section.

Reaction of 20 with base:

In a 25 ml. flask 0.34 (0.001 mole) 20 was dissolved in 6 ml. methanol and cooled to 0°. To this solution, keeping the temperature at 0°, was added 0.044 g. (0.0011 mole) sodium hydroxide. The solution was allowed to stir overnight at 0°. The reaction mixture was worked up in the usual fashion. Yield of 15 and 16 was determined to be 98% by n.m.r. spectroscopy. The 16/15 ratio was also determined by n.m.r. spectroscopy. The n.m.r. spectrum of the product has been given in the results section.

Methylene blue-sensitized photooxidation of 5:

A procedure adapted from van de Sande (1) was used for the photooxidation of 5. The apparatus used was described in detail by van de Sande and was used without any modifications. A solution of 1.0 g. (0.008 mole) 5 and 50 mg. methylene blue in 30 ml. methanol was placed in a water cooled photolysis cell. The pump was turned on and after equilization of pressure was reached, the cell was illuminated with two 200 watt frosted light bulbs, placed against the cell on either side. Oxygen uptake was slow for 3 hours when 220 ml., 110% theoretical amount of oxygen had been consumed. The solution was poured into 100 ml. water and extracted with ether (3 x 50 ml.). The ether extracts were combined, washed with water (50 ml.), washed with saturated sodium chloride solution (50 ml.), dried ($MgSO_4$) and concentrated. The resulting oil was analyzied by n.m.r. spectroscopy for the presence of allylic hydroperoxides 16 and 15. The n.m.r. spectrum has been described in the results section.

The above procedure was repeated with the addition of 0.1 g. 2,6-di-t-butyl phenol to the original solution before irradiation. The product was analyzed in a similar manner. The n.m.r. spectrum of the product mixture was described in the results section.

1-(Methyl-1-chloroethyl)-cyclohexyl iodide, 22:

To a 100 ml., 3-necked flask wrapped with aluminum foil, fitted with a drying tube, low temperature thermometer and addition funnel was added 3.1 g. (0.025 mole) 5 and 50 ml. ether. The solution was cooled to -40° and kept constant throughout the reaction. To this solution was slowly added 4.1 g. (0.025 mole) iodine monochloride. The solution was allowed to stir for a further 20 minutes and then allowed to warm to 0° at which time the reaction mixture was poured into 50 ml. water. The ether layer was separated, washed with water (3x50 ml.), washed with 10% sodium thiosulphate solution until colourless, dried ($MgSO_4$) and cooled to

-78°. Additional crops of crystals could be obtained by repeated coolings of the mother liquor. The yield of 22, m.p. 46.5-47.5, was 4.0 g. (56%). The sample of 22 prepared in this way was unstable at room temperature but could be stored in dry ice for indefinite periods.

The n.m.r. spectrum (CCl_4) showed absorption at τ8.2 (b) and τ8.05 (s). The signals were overlapping and no ratio could be determined.

Analysis of 22:

(a) Elimination reaction of 22:

The elements of iodine and chlorine were eliminated from 22 to yield the olefin by a method adapted from Stevens and French (55). A solution of 2.87 g. (0.01 mole) 22 dissolved in 10 ml. acetone was rapidly prepared and added in one portion to a solution of 1.66 g. (0.01 mole) potassium iodide in 50 ml. acetone. The solution was allowed to stir for an additional 10 minutes and then poured into 50 ml. water. The resulting solution was extracted with methylene chloride (3 x 50 ml.). The combined extracts were washed with water (50 ml.), washed with 10% sodium thiosulphate solution until colourless, dried ($MgSO_4$), and concentrated to yield 2.54 g. (82%) 5. The n.m.r. spectrum (CCl_4) of 5 was identical to that of the product 5 prepared via the reduction in liquid ammonia.

(b) Iodometric titration of 22:

Iodometric titration of 22 was carried out in the following manner. A carefully weighed sample of 22 (ca. 1.0×10^{-4} mole) was added to a solution of 30 ml. acetone and 2 ml. saturated potassium iodide. The mixture was left to react for 20 minutes at which time it was titrated with a standard sodium thiosulphate solution (0.02 M). The end point was determined by the discharging of the colour of the solution. The solution had to remain colourless for 10 minutes for the final end point determination. After subtraction of a blank, the iodine liberated was calculated. The titration gave 93.1% of

the iodine released.

Attempted preparation of 1-(methyl-1-chloroethyl)-cyclohexyl hydroperoxide, 21:

Method A:

In a 100 ml. flask was added 10 ml. ether, and while keeping the temperature at -40°, 3 ml. 98% hydrogen peroxide was added. To this solution, 0.287 g. (0.001 mole) 21 was added keeping the temperature throughout the reaction at -40°. Finally, 0.222 g. (0.001 mole) silver trifluoroacetate, dissolved in the minimum amount of ether, was slowly added. An immediate reaction was noted by the appearance of a yellow precipitate. The solution was allowed to stir for a further 10 minutes after which it was allowed to warm to 0°. The resulting mixture was worked up by the following general scheme. The reaction mixture was filtered through a celite pad and the resulting solution was washed with water (3 x 50 ml.), dried ($MgSO_4$) and concentrated. The resulting oil was crystallized at -78° from isopentane, giving a low melting solid with n.m.r. spectra identical to 16. The n.m.r. spectrum of the crude oil has been described in the results section.

Method B:

In a 100 ml. flask 5 ml. ether was cooled to 0° and 5 ml., 98% hydrogen peroxide was cautiously added at such a rate that the temperature did not rise above 10°. The solution was held at 0° during the course of the reaction. To this solution was added 0.287 g. (0.001 mole) 22 dissolved in 2 ml. ether. Finally, 0.333 g. (0.0015 mole) silver trifluoroacetate, dissolved in the minimum amount of ether was slowly added. A yellow precipitate immediately formed. The mixture was allowed to stir at 0° for a further 10 minutes after which it was worked up in the manner outlined in Method A. The product was analyzed by n.m.r. spectroscopy which has been described in the results section.

The product obtained was treated with base and the resulting product mixture was analyzed by n.m.r. spectroscopy for allylic hydroperoxide. The n.m.r. spectrum of the product has been described in the results section.

Method C:

A solution of 20 ml. ether, containing 6 ml., 98% hydrogen peroxide and 0.287 g. (0.001 mole) 22 at -40° was prepared as in Method A. To this solution was added a slurry of 0.32 g. (0.0015 moles) mercuric oxide in 2 ml. ether, maintaining the temperature at -40°. No change in the reaction mixture was noted. The solution was allowed to warm to 0° over a period of 1 hour and stirred at 0° for an additional 0.5 hour, at which time an orange precipitate was formed. This solution was then worked up as in Method A. Isopentane (20 ml.) was added to the crude reaction mixture and the resulting solution was filtered and concentrated to yield a clear oil. The product mixture was analyzed by n.m.r. spectroscopy.

Method D:

A solution containing 10 ml. ether, 10 ml., 98% hydrogen peroxide and 0.287 g. (0.001 mole) 22 was prepared as outlined in Method B. To this mixture was added 0.32 g. (0.0015 mole) mercuric oxide, slurried in 2 ml. ether. An orange precipitate immediately formed. The solution was allowed to stir at 0° for an additional 45 minutes and was worked up as in Method C. The product was again analyzed by n.m.r. spectroscopy which has been described in the results section.

The crude products obtained from the mercuric oxide reactions were combined and treated with p-nitrobenzoyl chloride by the method outlined for the preparation of 20. The crude product was recrystallized from Skelly B and analyzed along with the residue obtained from the concentrated mother liquor by n.m.r. spectroscopy. These n.m.r. spectra have been described in the results section.

The residue from the mother liquor was treated with base in the usual fashion and the product mixture so obtained was analyzed by n.m.r. spectroscopy.

1-(Methylvinyl)-cyclopentanol, 24:

The method used for the preparation of 6 was incorporated to prepare 24 from 72.6 g. (0.60 mole) 2-bromopropene, 14.60 (0.60 mole) magnesium turnings and 50.4 g. (0.60 mole) cyclopentanone in 600 ml. THF. The distilled product, b.p. 72-75° (18 mm.), $n_D^{26.3}$ 1.4745, was obtained in a 50% yield (38 g.).

The infrared spectrum (neat) showed absorption at 3360 (O-H stretch) and 1640 (C=C stretch).

The n.m.r. spectrum (CCl_4) showed absorption at τ5.05 (s), τ5.2(m), τ7.1 (b) (which disappeared upon exchange with deuterium oxide), τ8.2 (d, J = 1 cps) and τ8.3 (broad singlet), ratio 0.75:1:1:12.8, required 1:1:1:11. The areas of the peaks at τ8.2 and τ8.3 were combined.

Analysis: Calculated for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 75.94; H, 10.81. The mass spectrum gave a peak of m/e: 126 (P).

Isopropylidenecyclopentane, 23:

The procedure used for the preparation of 5 was used to prepare 23 from 15 g. (0.65 mole) sodium, 37.8 g. (0.30 mole) 24 and 30 g. (0.64 mole) ethanol in 400 ml. liquid ammonia. The yield after distillation was 16.5 g. (50%) of 23, b.p. 133-134°, n_D^{22} 1.4574. Reported (41) b.p. 135.5 - 137.5°, n_D^{20} 1.4585.

The infrared spectrum (neat) showed absorption at 2950 (C-H stretch), 1440, 1430, 1365 and 1090 as in reported (41) spectrum.

The n.m.r. spectrum (CCl_4) showed absorption at τ7.85 and τ8.45 (d, J = 1 cps with overlapping m), ratio 2:5, required 2:5.

1-(Methyl-1-bromoethyl)-cyclopentyl hydroperoxide, 25:

The procedure described for the preparation of 7 was used to prepare a crude sample of 25 from 11.2 g. (0.10 mole) 23, 14.5 g. (0.05 mole) 1,3-dibromo-5,5-dimethylhydantoin and 17.0 g (0.5 mole), 98% hydrogen peroxide in 60 ml. ether. The residual oil, 26.4 g.,had 73% of the theoretical hydroperoxide content.

The n.m.r spectrum (CCl_4) showed absorption at τ3.35 (b) (which disappearaed upon exchange with deuterium oxide), τ8.1 (b) and τ8.15 (s), ratio 1:18, required 1:14.

Reaction of 25 with base:

The base elimination reaction of 25 was carried out in the usual fashion. A solution of 2.23 g. (0.01 mole) 25 in 6 ml. methanol was treated with 0.44 g. (0.0011 mole) sodium hydroxide in 1 ml. water and 3 ml. methanol at 0° for 1.5 hours. The resulting solution was worked up as previously described. The product mixture, 1.2 g. of an oil, was analyzed by n.m.r. spectroscopy which has been described in the results section.

Reduction of 1.2 g. of the product mixture by 1.2 g. $LiAlH_4$ in 80 m. ether was carried out as described for the reduction of 16. The product obtained after work up with 10% potassium hydroxide solution was analyzed by n.m.r. spectroscopy.

Methylene blue-sensitized photooxidation of 23:

The procedure described for the photooxidation of 5 was used to oxygenate 1.0 g. (0.009 mole) 23 in 30 ml. methanol, containing 50 mg. methylene blue. Oxygen uptake was rapid and after 45 minutes, 265 ml., 115% of the theoretical oxygen had been consumed. The oil, 1.1 g. after work up was analyzed by n.m.r. spectroscopy.

Determination of the position of the O-OH peak in the n.m.r. spectra of 7, 8 and 9:

The n.m.r. spectra of 7, 8 and 9 were recorded as described by Richardson (58). Samples used for n.m.r. spectroscopy were freshly crystallized and free of any traces of water. Known weights of halohydroperoxides were dissolved in DMSO (d_6), dried over freshly baked molecular sieves, and the n.m.r. spectra of these samples were recorded. The sample compositions along with the positions of deuterium oxide exchangeable peaks are given in Table III.

Rate of reaction of 7 with base:

To a solution of 0.954 g. (3.88×10^{-3} mole) 7 dissolved in 24 ml. methanol and cooled to 0°, was rapidly added with stirring, a solution, also at 0° of 4 ml., 1.6 N sodium hydroxide and 12 ml. methanol. p-Dimethoxybenzene was added as an internal standard. At reaction times of 0.5, 1.5, 3, 5, 10 and 17 minutes, a 5 ml. aliquot of the reaction mixture was quickly quenched with a solution of 0.5 ml. acetic acid in 2 ml. water. Each sample was then worked up in the usual fashion and the product mixture was analyzed for the allylic hydroperoxides by n.m.r. spectroscopy. The results of this experiment were given in the preceding text.

Rate of reaction of 3-bromo-2,3-dimethyl-2-butyl hydroperoxide, 11, with base:

The rate of reaction of 11 with base was accomplished by a method similar to the one described above. A solution of 0.7420 (3.766×10^{-3} mole) 11 in 24 ml. methanol was cooled to 0°. To this solution was added in one portion a mixture of 12 ml. methanol and 4 ml., 1.6 N sodium hydroxide cooled to 0°. p-Dimethoxybenzene was added as internal standard. At reaction times of 0.5, 2, 5, 10 and 60 minutes, 5 ml. aliquots of the reac-

tion mixture were rapidly withdrawn and quenched in a solution of 1 ml. acetic acid in 2 ml. water. The samples were worked up in the usual fashion. The residue from each sample was analyzed for the disappearance of 11 and formation of allylic hydroperoxides by n.m.r. spectroscopy. The results are found in Table IV.

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